THE STUFF WE'RE MADE OF

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"... The web of being, blindly wove
By man and beast and earth and air and sea,"
SHELLEY, *Adonais*, stanza 54

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FOREWORD

FOR many years, in fact since the time of Darwin, Biology has provided the public with a picture of the world as it seems to the student of Life; more recently we have had the opportunity of hearing the opinion of physicists about the appearance of their universe; but, perhaps because of its comparatively late arrival, the science of Biochemistry—the meeting-place of the animate and inanimate worlds—has so far not attracted the attention that its intrinsic importance demands. It is our object to survey with the reader this still unfamiliar region between the physical and the biological sciences.

This book is not a Baedeker guide, exhaustively—and perhaps exhaustingly—listing every object within view; it seeks rather to indicate the general appearance of the countryside. We shall draw attention only to objects of special significance in the landscape, neglecting the vast mass of detail which, however important to the professional biochemist, would here tend only to distract us from our main purpose.

It is natural, and indeed inevitable, that Biochemistry should have developed only recently. Real progress in this science was impossible until some of the more fundamental problems of Physics and Chemistry had been solved, and in the meantime, the biologically-minded were attracted by the more obvious problems concerning the genesis, growth, and activity of individual animals, and the origin and relationship of species. But this lag in the development of Biochemistry has had an unfortunate consequence; the universe seemed to fall into two parts, the physical and the biological, the mechanical and the vital. In studying the chemistry of living tissues, we find ourselves in both worlds at once. To the biochemist, neither the biologist's nor the physicist's universe is altogether strange.

The main object of this volume is to give what would seem, in the present state of our knowledge, to be a reasonable

description of the relation of the living to the non-living. A secondary object has been to present to the reader some account of the remarkable advances recently achieved in Biochemistry itself, and to indicate the significance which this relatively new field of knowledge possesses for the future well-being of mankind.

The plan has been to discuss various topics, not all perhaps strictly biochemical, but all having some bearing on the principal object of the book. A few technicalities were unavoidable, but, by collecting most of these into Chapter XIV,* it has been possible to leave the rest of the book relatively free of elaborate formulae. The reader who wishes may safely skim this chapter, or even omit it altogether.

In a book such as this, it is clearly impracticable to give complete references to original authorities. Here and there the name of an investigator has been mentioned, but the choice of these names has been made almost at random, according to the convenience of the text. The few references given do, however, indicate the international character of biochemical, as of all scientific research.

During the writing of the book we have had the advantage of the advice and criticism of our colleagues in the University, and the Laboratory of the Royal College of Physicians, Edinburgh, and for all their valuable suggestions we wish to acknowledge our indebtedness. Also we wish to thank Mr. Walter Spragg, now of the Low Temperature Research Station, Cambridge, who gave invaluable assistance in the preparation of the MS.

Our thanks are due to Lt.-Col. W. F. Harvey, Dr. Walter Tebrich, and Mr. Robert White, S.S.C., for the use of certain unpublished photographs, and also to many authors and societies for permission to include illustrations from their publications. The sources of these will be found under the figures.

September 1938

W. O. K.
P. E.

* Chapter XVI in 2nd Edition.

FOREWORD TO SECOND EDITION

THE eight years that have elapsed since the first edition of this book was published have for the most part been occupied with the waging of a great world war. Biochemistry has played a part, though perhaps, compared with some other branches of science, a minor part, in this great drama. The progress of biochemical knowledge has no doubt been slower than it would have been if the Second World War had not occurred, and yet the accumulation of facts and the extension of fundamental knowledge has gone on apace. The massive volumes of the *Annual Review of Biochemistry*—every year some seven or eight hundred pages of concentrated, summarized, sometimes desiccated biochemical facts—testify to the enormous amount of research that has gone on in spite of all the distractions and difficulties.

With a book of this nature, it is fortunately not necessary to incorporate, or even to refer to, the great mass of highly technical knowledge which constitutes the main fruit of recent biochemical research. Only where some major feature of the landscape has been substantially modified, must we take note of the change: we need not draw attention to every little detail that has been altered. Any actual misstatement, of course, any remark in the first edition which further experience has shown to be wrong, has been amended or eliminated; but we have introduced new matter only when it seemed of first-rate importance, or when it possessed some unusual interest of its own. Sometimes both reasons combined to justify the new material.

The new edition contains two chapters more than the first. The rapid and important developments in our knowledge of the vitamins and other growth factors could scarcely be passed over, and it seemed convenient to divide the single chapter previously given to the topic into two. The other new chapter

is a short one in which an attempt is made to sketch the manner in which a muscle may actually work. Here we may be blamed for indulging rather too freely in somewhat fanciful speculation, but the problem of muscle contraction is a focus of much biochemical research and perhaps the reader may the better appreciate the significance of our present fragments of knowledge if he is helped to arrange these into some general scheme, however hypothetical, and so effect a provisional integration of the parts into a whole. We trust the crude picture we have suggested of muscle contraction may be helpful to the novice and not too obviously ridiculous to the expert.

W. O. K.
P. E.

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CHAPTER I

A SENSE OF PROPORTION

WHEN Gulliver visited Lilliput, he found himself in a country peopled by beings entirely similar to the men and women with whom he was familiar, except that they were only about one-twelfth of the size. They were miniature human beings, perfect in proportion, living in a miniature world, with everything in it—houses, furniture, clothes—all suited to their size. These minute creatures in their own world were just as much at home as Gulliver was in his.

Swift evidently intended his readers to picture the Lilliputian community as a small-scale model of an ordinary human society. Now, up to a point models will work very well indeed. The model engines of the nursery imitate tolerably well the real engines of the railways. Before a new ship is built models are constructed, and by examining their properties in an experimental tank an accurate idea is obtained of how the full-sized vessel will behave when it is built. The work of designing aeroplanes is likewise much assisted by knowledge derived from small-scale models. But the engineer must always be careful to use the model in the right way. He soon finds that he cannot simply multiply all his dimensions by some factor and assume that the new structure will behave just as the old one did. To do so would be to court disaster. It is easy enough to make a small paper glider which will float gently to earth when it is released. But substitute cardboard for paper and make every dimension ten times as great, and the large-scale machine will no longer behave so beautifully. Instead of gliding gently, it now crashes to the ground; for the weight has increased a thousand times, but the wing surface only a hundred times. The bigger the aeroplane, the more carefully must it be planned: the simple flat wings of

the paper model must be replaced by accurately designed ones of special cross-section, and the whole construction of the machine must aim at minimum weight combined with maximum strength. Gliding would be an easy sport to the Lilliputians, but the giants of Brobdingnag might never be able to enjoy this exhilarating pastime.

The mere size of a thing is, indeed, one of the most important facts about it. The design of a structure or piece of machinery is dependent on its dimensions. A small stream may be bridged by means of a straight, rectangular plank; but increase all the dimensions a thousand times and the stream which measured a couple of yards across becomes a great river about a mile broad. This could no longer be spanned by a straight wooden plank of correspondingly huge dimensions. Even if it could be constructed, such a bridge would break under its own weight. It does not help very much to use steel instead of wood; it is the *design* which must be altered. The cheapest method is to divide the bridge up into a series of separate small spans supported on a large number of pillars erected at intervals across the river—as, for example, in the Tay Bridge. The Forth, with its deeper channel, was not adapted for this kind of bridge; the much more interesting but also more expensive cantilever design was used instead.

Animate nature provides us with many examples of this general principle: that the size of a structure determines in large measure its design. A spider and an elephant are obviously as different from one another as the plank across the stream is from the cantilever bridge. The reader may remark that, after all, these two animals belong to two different classes, and some difference of structure is only to be expected. One is an arthropod and the other a mammal; and even animals of the same size but belonging to different classes exhibit a wide variety of structures. Agreed; but our point is that much of the difference between spiders and elephants is related directly to the difference in size. Imagine a spider enlarged so as to become comparable with an elephant

and at once you realize that the resulting creature would be impossible from the mechanical standpoint. The body, now ten million times its original weight, is still supported in the same pendant-like fashion, but on legs about two hundred times as thick; the strength of each leg, depending as it does

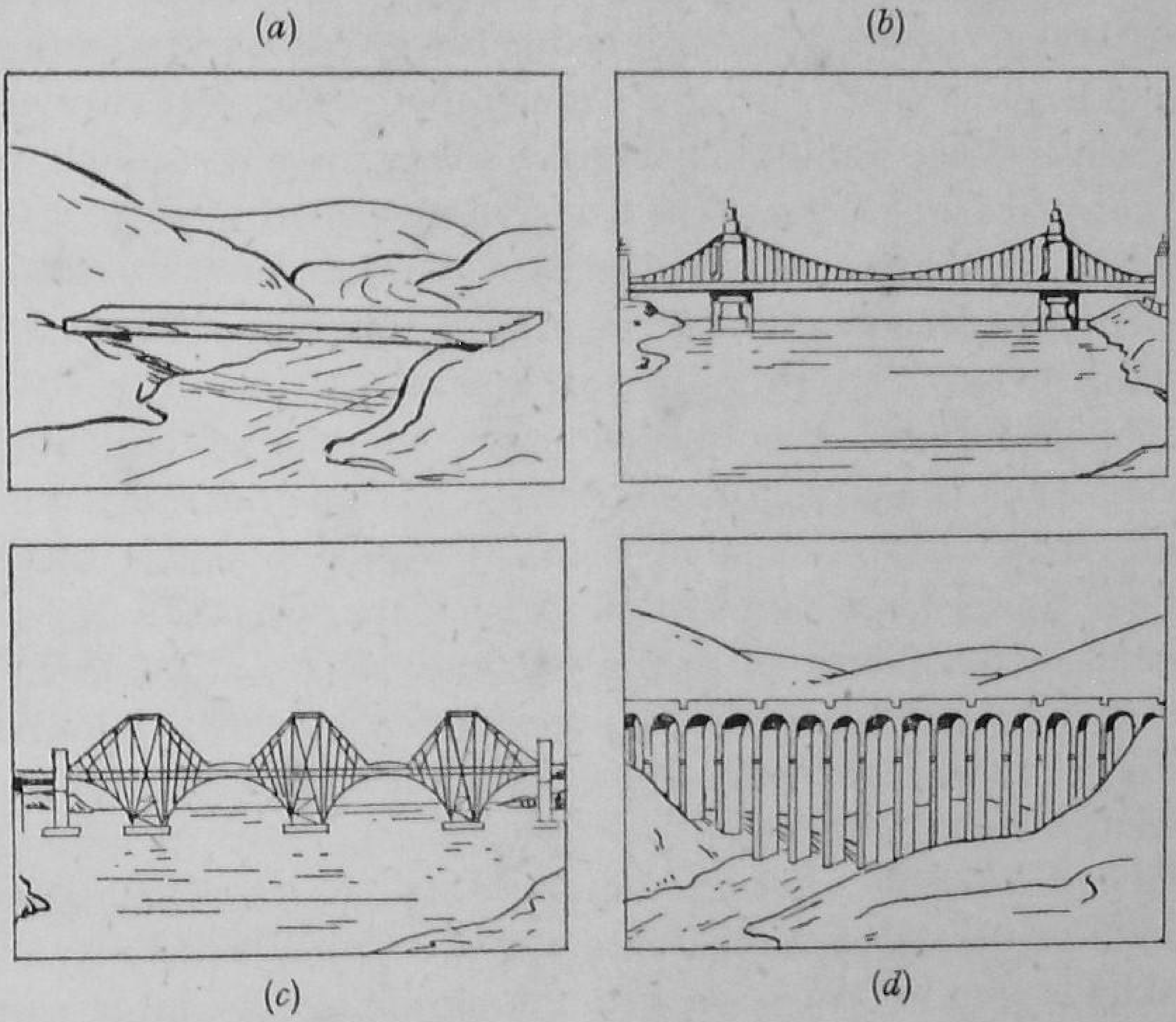

FIG. 1.—Illustrating how the design of a bridge depends on its size.

(*a*) A six-foot plank bridge.
(*b*) Hammersmith Bridge (686 feet).
(*c*) Forth Bridge (8,300 feet).
(*d*) Multiple span bridge.

on its cross-section, will be increased only forty thousand times—not at all in proportion to the weight it has now to support. The strain on the joints of the arch-like supports would be tremendous, and even if the muscles and tendons were strong enough not to snap, the heavy, straggly animal would be hopelessly slow and clumsy and altogether inefficient in the struggle for existence.

And now think of the opposite transformation—an elephant reduced to the size of a spider. The stout, cylinder-like creature supported on its relatively small base would be at a serious disadvantage when so diminished in size; with its short, stiff limbs, its rate of movement would necessarily be very slow, and it would find it very difficult to keep its balance, for, standing on a base so much smaller than the spider's, it would tend to be blown over much more easily by any gust of wind. Most small animals have either very short legs and a correspondingly low centre of gravity, like mice, or have widely spreading limbs, like spiders and flies.

The essential point may be put in this way. Whilst the weight of any body of a given shape increases with the cube of its dimensions, other important characters follow a different rule. Thus the strength of a sinew or a bone increases only with the cross-section, that is to say with the square of the linear dimensions. In other words, certain properties depend primarily on volume, others depend on surface, and so, though we may keep the geometrical proportions constant, a change of size will almost inevitably upset the balance from a mechanical point of view.

The size of an animal conditions not only its shape: it has much to do also with the nature of the animal's activity; as we have seen in connexion with the aeroplane, the problem of flight becomes more and more difficult as the size becomes very big. We should expect, then, that the weight of flying birds should be definitely limited. In point of fact, the heaviest bird which can really fly is the albatross, the weight of which is only about 30 lb. It is significant that many of the larger birds seem to have achieved their size only at the cost of abandoning wholly or partly the power of flight; very obviously is this the case with the heaviest bird of all, the ostrich.

At the other extreme there is evidently a lower limit below which the power of flight with wings begins to lose its especial advantages. Here we are no longer concerned with birds, for the lower limit to their size is set by other factors. In the

insect world, however, we find the power of winged flight continuing down to quite small sizes. Think of the dragon-fly, the bee, the house-fly, and the midge. Evidently at the lower end of the scale, wings are becoming relatively less worth the trouble involved. Midges are happy only in still air; it is hopeless for them to try to fly against a wind, and their small size puts them absolutely at the mercy of a storm if they ever venture up in one.

Quite a number of the smaller insects never fly; the flea, for example, jumps instead. Jumping for minute animals is a very efficient process: a flea can jump dozens of times its own height. Thus very minute living objects, if they take to the air at all, tend to depend on jumping or merely drifting or something other than the rather expensive device of winged flight.

The lower limit to the size of birds has nothing to do with flight. Birds are "warm-blooded" creatures, and if a bird were too small, it would find it difficult to keep warm. This is because cooling is a surface phenomenon, and the relative importance of surface becomes greater as the scale is reduced. Mammals, being also warm-blooded, are subject to the same restriction; and it is not an accident that the smallest mammal, the shrew-mouse, is of the same order of size as the humming bird.

If the difficulty of keeping warm has placed a lower limit to the size of birds, what sets the upper limit to the size of insects? All animals must respire: they must take in oxygen from their surroundings. We are familiar with the lungs of birds and mammals and with the gills of fishes, but insects have neither gills nor lungs—instead, they have a system of fine air tubes, opening on to the surface of their bodies, and the air works along these tubes by the process of diffusion. Now gases diffuse quickly over small distances, but where larger distances are involved the time taken is correspondingly longer. If we made an insect bigger and bigger a point would be reached at which this method of respiration could not keep

up the supply of air. Consequently we have no really big insects: the plan on which they are constructed is one that does not work on the big scale.

These are but a few examples of how the plan and structure of a particular variety of animal is definitely limited by its size. But the principle is a general one. Every group of animals (or plants) has a definite range in size, just because no member could exist and work efficiently outside this range. Single-celled animals are practically all microscopic; invertebrates are rarely more than a few pounds in weight; the largest land animals are evidently nearing their limit. The mammoth is already extinct and the elephant is forced into a form not specially elegant or efficient.

When we come to animals which live in water, we find that considerably greater sizes are attained. Whales may reach a hundred tons (as compared with the five or six tons of a large elephant), for here the effect of weight is to a large extent neutralized by the buoying action of the water. But even the largest monsters, living or extinct, are never more than perhaps one or two hundred tons and the relatively small number of kinds of such enormous beings shows that they are not very efficient forms of life.

It is highly probable that such monsters have approached the upper limit of size for life on this planet. What can be said of the lower limit? Perhaps the smallest objects which everyone would agree to call living are very minute bacteria, barely visible with a powerful microscope. One such bacterium is built up of perhaps a thousand million atoms, and it is unlikely that any structure much simpler could exhibit growth and reproduction and the other phenomena characteristic of life. It is probably safe to fix the lower limit of size for living things at not less than ten million atoms. The largest living things are about one million million million million (one quadrillion) times as great as these ultra-microscopic bacteria. Life is a phenomenon which would seem to be limited to this range in size—a range which is certainly a very wide one, but

nevertheless only a comparatively small fraction of the total range of known things.

Here it may be useful to tarry for a moment and try to see this question of magnitude in some kind of perspective. The very big and the very small are equally outside our powers of direct perception. It is not easy to retain a sense of proportion when dealing with the size of the electron or the distances of inter-stellar space. The huge figures which represent the number of atoms in a jug of beer or the distance of the nearest star mean nothing to us in terms of things with which we are familiar, for our direct, everyday experience ranges from objects like specks of dust and filaments of hair, to railway journeys or perhaps ocean voyages. From this direct appreciation of space as something we work in and move through, we extrapolate, partly by imagination, but more by arithmetic and mathematics, until we have a presumably true but yet ghostly notion of that larger and more mysterious universe which science has brought within our ken. Perhaps we can never feel quite at home in this roomy edifice; but by the help of analogies and, above all, by trying to keep a sense of relative values, of proportion, we do our best to make ourselves mentally comfortable.

One of the common devices for making a complicated group of facts look simple is to arrange them pictorially on a graph or according to some kind of scale. The pictures so obtained give a sort of concrete reality to relationships previously thought of only in somewhat vague and abstract terms. We want, then, to arrange all our objects on a scale according to their size, from the smallest known particles of matter, protons and electrons, on the one hand, to the whole universe on the other. Now, from what we have said above, this scale must be such as to bring out clearly one thing, the relative proportion of one object to another. This can be done quite simply by arranging that the distance apart of any two objects on the scale corresponds to the *ratio* of their sizes. Thus, if some particular point represents the weight of one egg and a point

one inch along represents ten eggs, then a point two inches from the first would represent one hundred eggs, and one thousand eggs would be denoted by a point one inch still further on. The salient characteristic of the scale is that one inch of it always corresponds to a ten-fold increase. (Of course, we might have chosen two-fold jumps or indeed any other as our basis; the choice of ten-fold is arbitrary, but happens to suit our present purposes.)

It is convenient to select as our unit of weight not an egg or even a pound weight, but the weight of one proton, the unit charge of positive electricity. This is practically the same as the weight of one hydrogen atom, for the latter consists simply of one positive unit charge and a negative one, that is, a proton and an electron, and the weight of the electron is only about one two-thousandth of that of a proton, and so is almost negligible in comparison. Now, all matter may be regarded as built up of approximately equal numbers of protons and electrons, so that the weight of any object in terms of the proton as the unit is practically equal to the number of protons it contains.* The weight, then, of a single proton (or a hydrogen atom), we may represent by zero on our scale (Fig. 2) and of ten protons by the point 1; the point 2 represents 100 protons, the point 3, 1,000 protons, and so on. Ascending the scale by one corresponds to multiplying the number of protons by ten. Thus the point 6 corresponds to 10^6 or one million protons. A red blood cell contains about one hundred million million, or 10^{14}, protons, so that its size will be represented by the point 14 on the scale; whilst a teaspoonful of water has in it about one million million million million, or 10^{24}, protons, and so is at point 24. A whale is at about point 32, the world is at 51·6 and the sun at 57. Of the other stars in the heavens, most of them are perhaps a little heavier than our own sun, but they are of the same order of weight, and so would be placed at about the same point.

* For this purpose the neutron may be regarded as one proton and one electron.

And now, it might be thought, having reached the largest star, we have surely come to the end of our scale. But this is by no means the case. The stars themselves are organized into huge stellar systems, of which our own galaxy, the Milky Way, is but one. The others constitute the spiral nebulae, each of which probably contains thousands of millions of stars, and which are separated by distances so great that light takes perhaps a million years to travel from one to its nearer neighbours. These nebulae, then, are the next objects to be placed in our scale, and as each contains 10^9 or 10^{10} stars they are to be put nine or ten units above the sun.

But we have not even yet made our last entry. We cannot, it is true, arrange these nebulae into groups or systems, each occupying a relatively densely packed fraction of the universe and separated from other nebular systems by practically empty space. There is no evidence of any such large-scale organization of these myriads of nebulae. They seem to form one system of incredibly huge dimensions. Millions of them can be seen by means of a powerful telescope and with each increase in the range of our instruments swarms of new ones come into view. Yet, however vast this system of nebulae

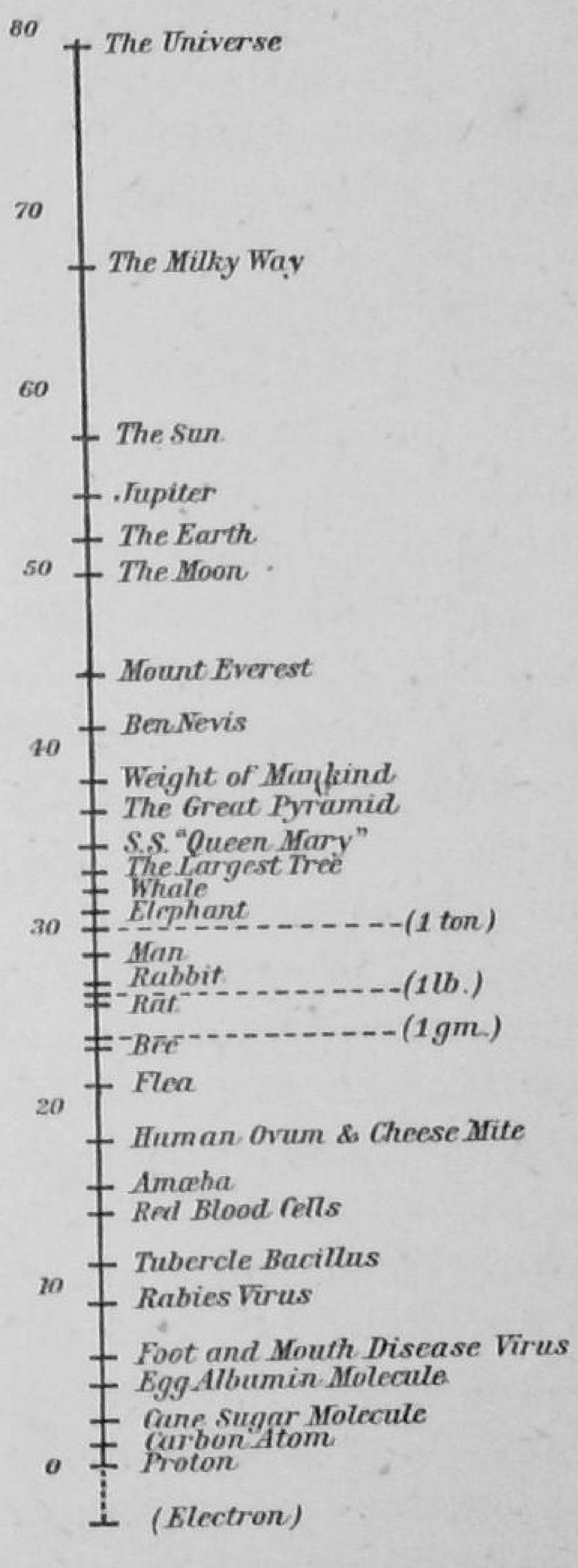

FIG. 2.—The Relative Sizes of Things. One unit on the scale represents a ratio of 10 : 1.

may be, there is reason to believe that it is not infinite, but that the number of individual nebulae is finite, even though it is very great; it has even been found possible to form an estimate of this number. Eddington has been led to the conclusion that there are about 10^{78} particles in the whole universe: that is to say, the weight of the universe will be about 10^{78} times that of a single hydrogen atom or proton. This is an unimaginably great number, but it is easily enough dealt with on our scale. We merely insert an entry at point 78 and mark it "the whole universe". As this must needs be the upper limit, the scale will run from the point 0 to the point 78. Within this range every object in the universe, and indeed the whole universe itself, can be represented—with the exception of the electron, to accommodate which the scale must be extended a few units in the negative direction.

In Fig. 2 we have placed various objects in approximately their correct positions. Up to about the point 10 or 12 we have atoms and molecules and various kinds of colloidal or sub-microscopic particles. Living cells appear at point 10, and between this and point 33 are located all the different plant and animal organisms, each according to its size. Above point 33 the entries become less and less crowded together—not that the number of individual objects of the kind in question is necessarily less, but rather that they are more uniform in type. In fact, they are less and less organized and so less differentiated from each other. Thus the stars in the universe can be classified into a few types, but amongst living beings on earth, perhaps in numbers comparable with the stars, we have at least hundreds of thousands of different species. At the lower end of the scale, again, the possibilities of complex organization are evidently restricted, this time simply on account of the small number of units involved. With two protons and two electrons, for instance, there would seem to be only two stable possibilities: one is the molecule of ordinary hydrogen and the other is the atom of an element, discovered a few years ago, called "heavy hydrogen" or "deuterium".

As we increase the number of units in a system its possible complexity and the number of distinct configurations which it may assume rapidly increase. They have become staggeringly great when the system is of the size at which organized life is just possible. Over the range 8 to 33, on our scale, we continue to encounter all kinds of examples of this power of matter to organize itself in highly complex aggregates exhibiting that peculiar stability and persistence so characteristic of life. But the only objects we know of above point 33 are all of a different type, unorganized and without individuality. Life is peculiar to a limited portion in our "mass spectrum" of the universe.

This "spectrum" is an example of what is called a "logarithmic scale"; such scales have been found of great service in many fields of activity. Thus, when the astronomer says that a star is of the "first magnitude" or "third magnitude", he is really using a scale of this type, though somewhat disguised, as his units are chosen rather differently. The wireless enthusiast measures the strength of the sound produced by his loud-speaker in "decibels". He too is using a logarithmic scale, in this case one very similar to our own, except that ten units instead of one correspond to a ten-fold increase in the energy of the sound. The great advantage of these scales for the recording of visual and aural impressions is that they correspond to an important physiological fact, namely, that alteration of the intensity of a sense impression by, let us say, 10 per cent has about the same apparent effect on our consciousness whatever may be the initial intensity of the impression. Thus, if in very dim light we are just able to perceive a 10 per cent change in intensity, then we shall also just detect a 10 per cent change in intensity in the case of a much brighter light. This principle holds only very approximately, but it is sufficiently true to be of great practical importance. It means that, on the logarithmic scale, equal intervals correspond to changes in sense impression which we should judge as being of equal value. To the unsophisticated observer the change from a star of the first magnitude to one

of the second appears roughly the same as the change from one of the second to one of the third. In the environment of an animal, it is the percentage, rather than the absolute, degree of change that really matters, and so it is not surprising that our consciousness seems to assess changes on a "percentage" basis; it works, in fact, on a logarithmic scale.

Reverting now to our scale of sizes, let us see how it helps us to keep a sense of perspective in dealing with objects of very different magnitudes. Let us fix our attention on four points at approximately equal intervals: an amoeba (15·5), a flea (21), a rat (26·5), and a whale (32). These are separated by intervals of $5\frac{1}{2}$ units; this means that each is about 300,000 times as heavy as the immediately preceding one. The flea would look to the amoeba much as the whale looks to the rat. Again, as the distance from the amoeba, a typical single cell, to the whale, is about 16·5 units, there must be about $10^{16\cdot5}$ cells in a whale (considerably more than the number of atoms in a cell). Or, again, the rat at point 26·5 is just about half-way between the hydrogen atom at point 0 and the whole world at point 52. This means that if the rat were magnified to become the size of the world, the hydrogen atoms in it would have grown to the size of the original rat. Plate I contains a series of objects separated from each other by 12 units on the scale; that is to say, each of them is a million million times as great as the following one.

Man appears at point 29 of the scale, and the range of his immediate experience of the universe, it may be observed, is limited to a relatively small distance on either side of this point. Of the very big and the very small he has no direct experience; he can only deduce their size by indirect and sometimes highly complicated reasoning. The stars and even the sun and moon are thought of by an unsophisticated primitive man as existing perhaps in a curtain or canopy a few miles above his head. The world, or rather that fraction of the surface over which he can roam, determines the upper limit of his conceptions of size. Similarly, he cannot conceive

of anything less than a speck of dust or a grain of sand. In other words, our immediate appreciation of space and matter reaches from about point 20 to about point 40, which is roughly a quarter of the total range of the scale. The very great and the very small are strange to us; we have no direct knowledge of their properties. Being acquainted with them only at second hand, we cannot comprehend them except by a peculiar and perhaps self-deceptive effort of the imagination; we are never really at home in these queer places.

In recent years it has become clear that these strange regions of the very big and the very small are really far stranger than anyone had guessed half a century ago. On the very big scale, space is no longer the kind of thing we intuitively conceive it to be; it is intrinsically curved, and the universe as a whole resembles the surface of a sphere rather than a flat sheet of paper. In the world of protons and electrons, on the other hand, the very idea of space becomes of doubtful validity. Precise location of these objects, it would seem, is not always possible. We can represent these fundamental entities by mathematical symbols and deduce their properties from fundamental laws, though real intuitive appreciation of them appears to be beyond us.

But we also meet other interesting changes as we traverse the scale. At the bottom end, in the region of atomic dimensions, it is the electrical forces which are all-important. Gravitation is almost wholly negligible in comparison. The electrical force, for example, between a proton and an electron is 10^{39}—a thousand million million million million million—times the gravitational force, and so it is the former which regulates the "planetary system" of the atom. But in the real planetary system of the sun things are very different. It is gravitation almost exclusively which governs the planets in their courses, and even the sun itself in its motion through the Milky Way; for the sun, under the aggregate attraction of all the other stars in the galaxy, sweeps along in the vast orbit which it takes thousands of millions of years to complete.

And at the upper end of the scale, in the world of the nebulae, the distances are so vast that the effect even of gravitation becomes negligible and the curvature of space is the dominating influence. The distant nebulae would doubtless be receding a little less quickly, the universe would be expanding somewhat less rapidly, if the constraining effect of gravitational forces were removed, but on this grand scale it is the inherent properties of the cosmos that count rather than the character of the matter which it may contain. To the tortoise, crawling about in the garden, a small rockery may present an almost insurmountable obstacle: the engineer planning a railway line is concerned mainly with the broad contour of mountain and valley: but for Marconi, wishing to bridge the Atlantic by wireless, the principal consideration was the curvature of the earth; for his purpose the details of topography could safely be neglected.

But between the region of atoms on the one hand and of solar and stellar systems on the other, there is a broad intermediate zone (roughly between points 10 and 40) where electrical forces and gravitational forces meet each other on approximately level terms.

It is with this zone that we are most directly familiar, for the life of each of us begins at a size corresponding to point 15 on the scale and finishes at about 28 or 29. Here it is that we live and work, and play our little part upon the stage. Of all the features of this intermediate region the most interesting and characteristic, and at the same time the most mysterious, is undoubtedly the phenomenon of life. We want to understand how living things are related to the rest of the universe; how they are constructed, how they work; and how far, in their intermediate position between the very big and the very small, they owe their remarkable properties to the fact that they are able to make the best of both worlds.

Already in our discussion of the effect of size on form and function, we have remarked on the great importance of the ratio of surface to volume, and on the fact that as size decreases

those forces which depend on surface or cross-section become ever more decisive in their effects. This principle holds not only for a series of structures of the same type; it applies broadly to the universe as a whole—at least over a wide range in our scale. For really large things, such as the sun or the earth, the surface forces are practically negligible. In the case of ordinary large animals or plants surface is perhaps more often deficient rather than over-abundant—plants, for instance have to enlarge their surface specially in the form of leaves to enable them to absorb sufficient energy from the sunlight to meet their needs. It is when we come to objects of the dimensions of a single cell—below point 16 on our scale—that we begin to find surface effects playing a really important role.

But this increasing importance of surface cannot go on right down to the point 0. For in the region of single atoms and molecules the idea of surface is not relevant. An atom of hydrogen or a molecule of carbon dioxide has no surface in the usual sense, any more than the solar system can be said to have a surface.

Evidently, then, there is a range in our scale over which surface is of special importance. This range, from perhaps point 5 to point 10, is the home of the "colloids". Here behaviour is dominated by the great importance of surface and of the forces associated with surfaces. So peculiar are the phenomena which come to light in this region, the region between atoms and molecules on the one hand and ordinary microscopic objects on the other, that a special science has been called into existence to deal with it. This is the science of colloidal chemistry, and its proper development is obviously essential if we are ever to advance far in our understanding of the phenomena of life. We are all essentially bundles of colloids soaked with water and strung round a bony framework to give form and support. It is amongst the colloids that we reach perhaps the most complex phenomena of the inorganic world; it is significant that it is in the colloidal range somewhere

between points 6 and 9 that the phenomena characteristic of life first appear.

Let us look again at our scale and run through it with this

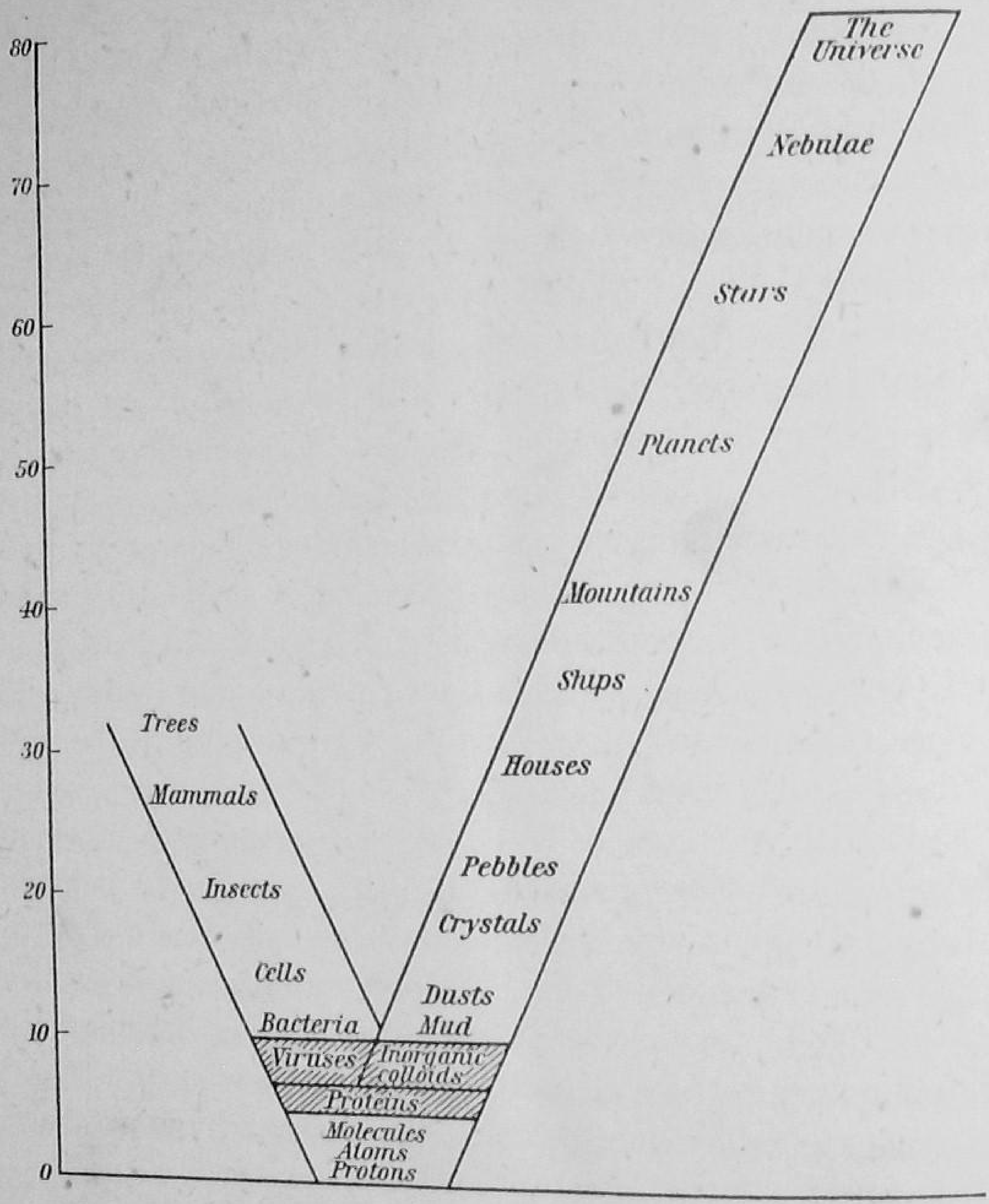

FIG. 3.—Illustrating the relation between animate and inanimate worlds. The same type of scale is used as in Fig. 2.

idea in mind. Starting at the bottom, we pass through the region of atoms and simple molecules, and then on to compounds of increasing molecular size. Insensibly we enter into the domain of the colloids, and it is at this point that the great bifurcation occurs (see Fig. 3). Along the main route

we are already beyond the point of greatest complexity. Sand-grains, rocks, planets, and even stars, these present problems difficult enough in all truth, but they are of a lower order of complexity than those which would be involved in the complete description of a protein molecule. Along this main branch, increase in size does not involve increase in organization, but rather the contrary. The behaviour of these large objects is usually not dependent on their detailed structure. If a boulder weighing a ton falls on your head it does not matter much whether it is made of granite or sandstone.

This main branch—the ordinary physical inorganic world—extends without interruption right to the top of the scale. But the other branch is very different. As we proceed along it from point 12 to point 33, we encounter phenomena which, broadly speaking, are of constantly increasing complexity. Here we have objects which grow and reproduce their like. They react to their environment in a characteristic fashion, protecting themselves against harmful influences and attempting to complete their natural development in spite of all adverse circumstances. They show what looks like spontaneous activity, and as we go up the scale the spontaneous movements become more obviously directed to specific aims. And so we find emerging the phenomena of emotion and will and thought; in the lower animals in only rudimentary forms, but in man as a prominent and characteristic feature. But this branch series soon comes to an end; for sizes much above 30, it would seem, are incompatible with the strange kind of organization we call life.

In our scale, then, we have a picture of the whole universe, both physical and biological. What do we know about it in detail? How are the phenomena characteristic of the branch series, the phenomena of life, related to the properties of the inorganic world? What, indeed, is life? It would be futile to hope for a complete answer to these questions. Science has made great strides, but it can still perceive things only through a glass, darkly. We may hope for a clearer light, but are we

sure that even with the best illumination we should be able to see all we should like? The scientific method has yielded much—but it may have limitations. Before proceeding to the discussion of various special aspects of the structure and behaviour of living things, let us consider the broader aspects of the question. Let us inquire what the scientific method really is, what sort of purpose it may be expected to fulfil, what kind of question it can answer.

CHAPTER II

THE SCIENTIST TAKES A SAMPLE

AMONGST our friends and acquaintances, there are some whose views we regard as eminently sound and reliable, and others we consider untrustworthy in their judgment. We are, of course, aware that the "sound" person is not always correct, nor is the other invariably wrong. We cannot guarantee beforehand the rightness or wrongness of any particular statement which may be made by either. What we can guarantee is that of all the statements made by the reliable man, a large proportion will be correct; whilst of those made by the unreliable one, a large proportion will be wrong. We may imagine that the former imposes on himself some rule which ensures that not more than, say, 1 per cent of his statements will be wrong. His statements may then be said to have a reliability, or, to employ a useful expression, a "confidence value", of 99 per cent.

This idea of the "confidence value" of a class of statements or data is of the greatest importance both in theory and in practice. A confidence value of 100 per cent would, of course, mean absolute certainty. But in making our decisions regarding those things which really matter in life, as well as about those which do not, the data we have on which to base them rarely have confidence values of 100 per cent. And so it is even in the realm of science. We want the confidence values of all our statements to be as high as possible, but absolute certainty is rarely, if ever, attained—at least where precise and definite statements are concerned.

This brings us to the consideration of the other essential feature of a statement, namely, its meaning or, more precisely, its content. It is quite clear that it is not difficult to ensure that all our statements may have a confidence value of 100

per cent if we make them sufficiently vague and indefinite. We may, for instance, say that a fly weighs less than 1 lb. or that the English Channel is between five and one hundred miles wide, and be quite sure that we are absolutely correct: but we are also saying nothing useful. The more precise we make our statements, as for example by narrowing the limits within which we assert the weight of the fly or the width of the Channel to lie, the less confidence can we attach to them, until finally if we make the absolutely definite statement that the English Channel is exactly twenty miles wide, we may be practically certain that the statement is wrong. It will thus be seen that there is a definite antagonism between the content of the statement and its reliability.

In science, we want statements with the highest possible content *and* the highest possible reliability. But the more we have of the one, the more difficult does it become to keep the other. We can have both butter and jam, but the bigger the share of butter, the smaller our portion of jam. It is the business of science to maximize both content and reliability, and so, as it were, to have the best of both worlds. Scientific method may be regarded as a technique for achieving this object.

Let us look at this conflict between content and reliability a little more closely. In order that a statement should have high content, it is necessary that it should be capable of some kind of general application and that its meaning should be precise and quantitative. Thus we may regard the statement of the law of gravitation as possessing high content. This law states the force with which any one piece of matter in the universe attracts any other. It is universal in its application, and is precise and accurate in a quantitative sense.

Now, as was quite natural, the earliest discoveries in the development of modern science referred to inorganic nature. They dealt with the movements of the planets and the properties of matter. The conclusions arrived at possess wide applicability almost automatically. What is true for one piece of copper or one sample of pure water is presumably true of

all others—provided that attention has been concentrated on essential and not accidental features of the piece of matter in question: the shape of the water in a bucket is obviously not a property of the water but of the bucket. In these circumstances, the chief errors which arise are those due to careless observation and inaccurate measurement. It is therefore not surprising that in the early development of science, and indeed in physical science generally, prominence should have been given to this type of inaccuracy. To deal with it in a systematic way mathematicians developed the theory of Errors of Measurement. This recognized the essential inaccuracy of all quantitative observations, and its object was to maximize the reliability of conclusions based on such imperfect data.

But with the growth of the biological sciences, a new type of error has come to the forefront. If we want to know the effect of insulin on the rabbit, the only practical method is to administer it to a few rabbits and observe the result. In other words, we take a sample of the whole population of rabbits and, on the assumption that this sample does, in fact, fairly represent the whole population, we form our conclusion about the effect of insulin on rabbits in general. But we know quite well that all rabbits are not alike. It is possible that all our experimental rabbits might by chance have been abnormal ones. Our conclusion might, in consequence, be quite wrong and valueless when extended to the whole population. Thus we reach the idea, very important in biology, of the Error of Sampling.

It is to be noted that this Error of Sampling is essentially connected with the desirability of making statements of wide applicability. It does not arise at all if we word our statement so as to refer to the sample actually observed; but such a statement would usually possess little or no interest or value, unless our "sample" amounted to practically the whole population. But, in practice, this method of eliminating the Error of Sampling is usually quite impossible, for we cannot collect all the rabbits in the world so as to test the substance on them.

We are thus on the horns of a dilemma. Large samples are impracticable, small ones may not be representative. The best we can do is to make the samples as large as possible, and then try to find by what method we can extract from them the maximum amount of information about the population as a whole. Clearly, a theory of sampling is required, analogous to the theory of Errors of Measurement already referred to. This theory should tell us how to make statements, based on the sample, about the general population—statements having the maximum precision compatible with a given degree of reliability.

Let us note, first of all, that the whole problem of sampling arises because the individual rabbits are not all absolutely identical with each other, and, secondly, that what we are interested in and want to make statements about is not any individual rabbit but the whole population of rabbits. Now, whereas in respect of one character an individual is described by a single measurement (if the character be quantitative, *e.g.* weight) or by a single adjective (if it be qualitative, *e.g.* colour of hair), in the case of a population it is different. Here a single character gives rise to a "frequency distribution". It is worth while spending a little time so that we may understand exactly what this expression means.

Let us suppose that we are interested in the height of men living in England. If we take up a book of reference which gives us information on this subject, we may expect to find a statement of the average or mean height, which might, for instance, be 5 ft. 7 in. "Mean height" is a very important character; but we know, of course, that all Englishmen are not even approximately 5 ft. 7 in. Some are taller, some shorter than the average. There will doubtless be more individuals with heights between 5 ft. 6 in. and 5 ft. 8 in. than between 5 ft. 4 in. and 5 ft. 6 in. or between 5 ft. 8 in. and 5 ft. 10 in. There will be very few dwarfs and very few giants. We might, in fact, give a pictorial representation of the state of affairs by means of a diagram such as that shown in Fig. 4.

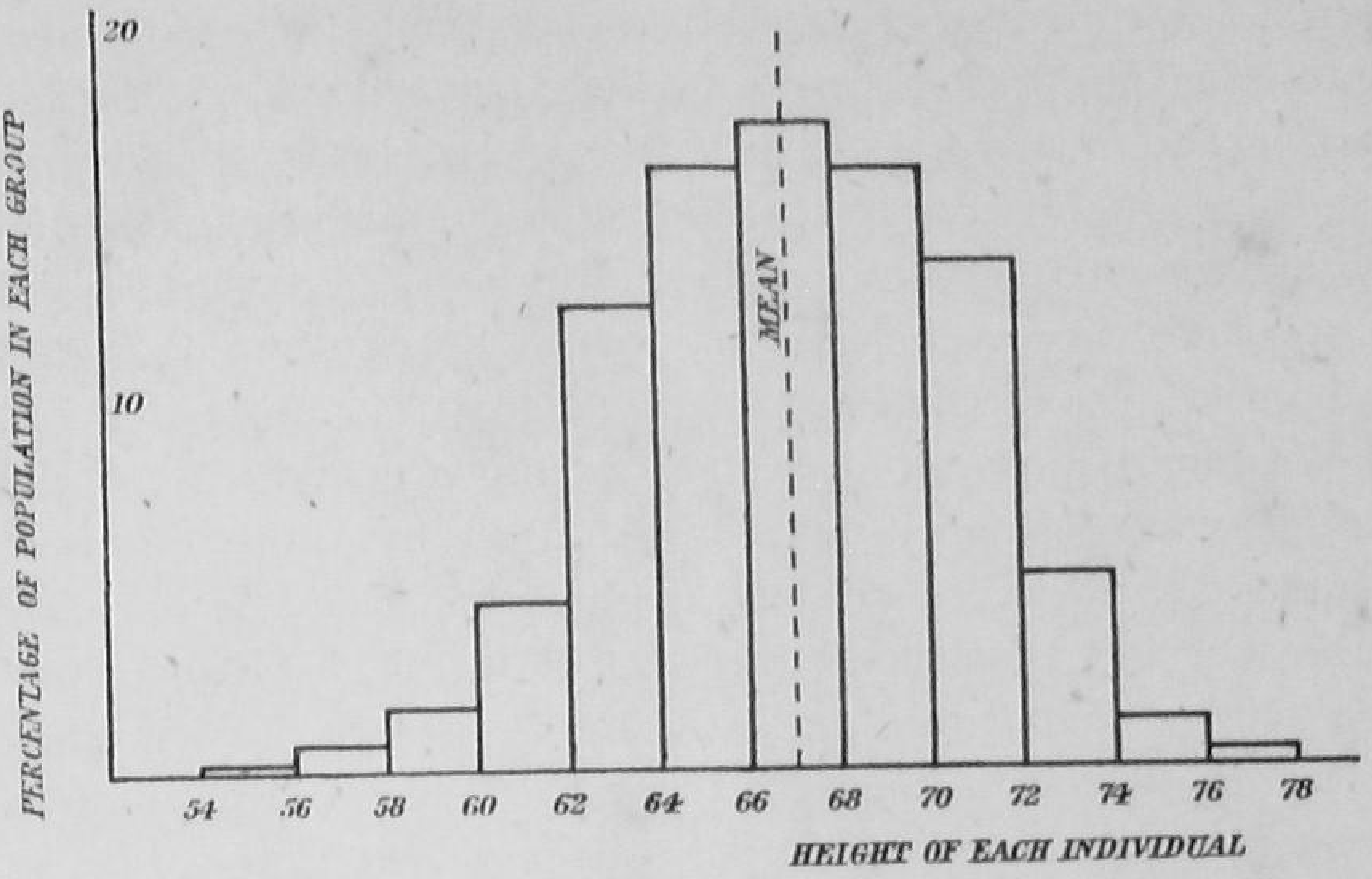

FIG. 4.

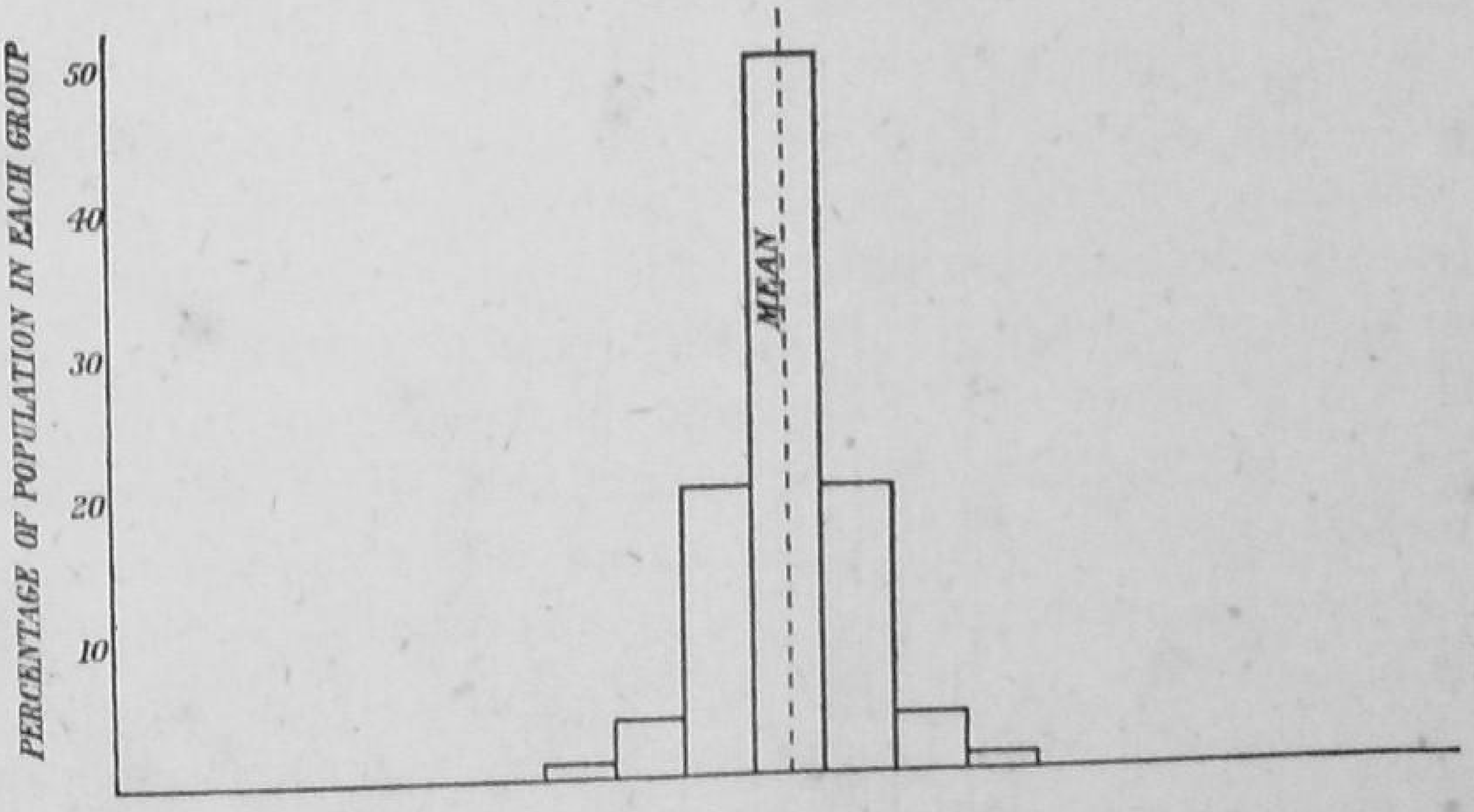

FIG. 5.

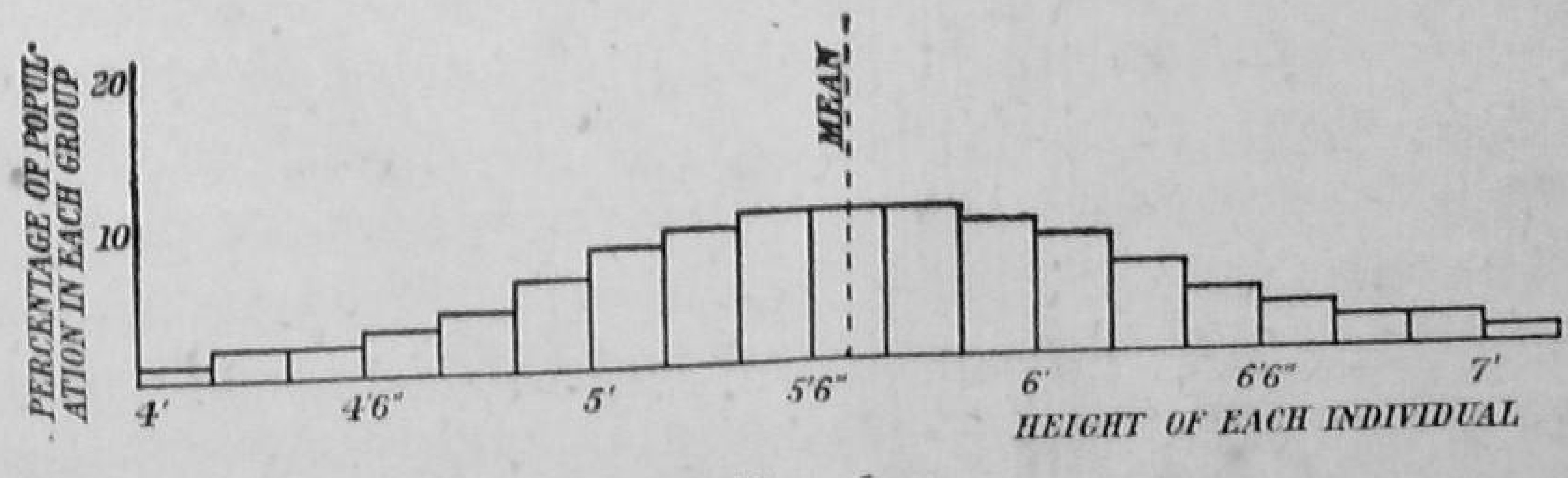

FIG. 6.

The horizontal line or axis represents height and is divided into equal units each corresponding to two inches. On each two-inch unit as base we may draw a rectangle, the area of which is proportional to the number of men whose heights lie within the particular two inches in question. We thus obtain a step-like curve which is very low at its extreme ends and is highest over the range of 5 ft. 6 in. to 5 ft. 8 in.

We might, however, have two populations both with the same average height, but characterized by quite different "frequency charts". The chart might, for instance, in extreme cases look like that shown in Fig. 5 or in Fig. 6. In one case the heights of half the population lie between 5 ft. 6 in. and 5 ft. 8 in., whilst in the second case the corresponding figures are 4 ft. 8 in. and 6 ft. 6 in. Clearly in the first case (Fig. 5) the population is approximately homogeneous in respect of height; in the second (Fig. 6), the degree of variation, or "scatter", is very great. Thus the two populations, although agreeing in respect of mean height, differ very markedly in respect of variability. We see that in characterizing populations it is necessary to state not only the average or "mean", but also the degree of variability or "scatter". Statisticians use the word "parameters" to denote quantities such as "mean" and "scatter" which describe populations. Fig. 7 shows the "mean" and "scatter" of a population of a thousand rabbits in respect not of height but of the concentration of sugar in the blood.

We are now in a position to give a more exact statement of the problem met with in biology. We have to make our observations and measurements on a sample—often a small sample—of the whole population. This sample will have a certain "mean" and a certain "scatter". But, clearly, it would usually be wrong to attribute to the general population precisely these values of "mean" and "scatter", for successive samples will differ from each other and only occasionally will their means and scatters agree even approximately with the corresponding parameters of the general population. At the

same time, it is clear that the sample would tell us *something* about the general population. Common sense and common experience assure us of this. In everyday life, we are constantly, with more or less success, making judgments based on samples. The scientific problem is to find a definite rule

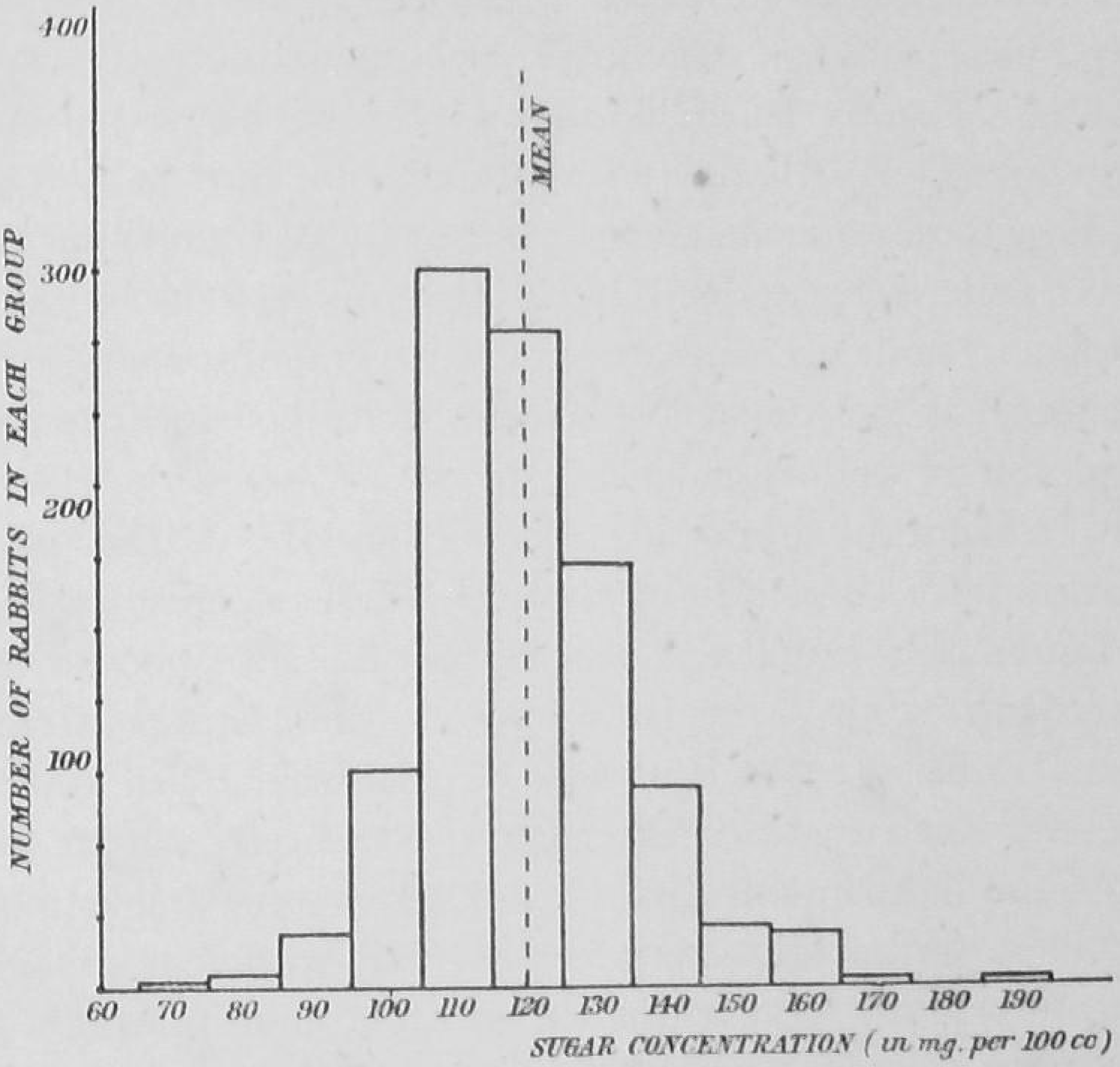

FIG. 7.—Showing the "mean" and "scatter" in a population of 1,000 rabbits, in respect of blood-sugar concentration. (From data collected by E. L. Scott, *J. Biol. Chem.*)

according to which statements possessing a certain degree of reliability, or confidence value, can be made, from a sample, about the general population.

This is the problem as it confronts the biologist or the biochemist or the psychologist, or any scientist who studies living beings. But in reality it is only a special case of the general problem of science. We all know of the two logical methods of induction and deduction. In deductive logic we are given the general principles and from these we deduce

particular cases. When we employ induction we start with particular cases, particular facts of observation, and from these attempt to arrive at general principles. One characteristic feature of modern science is its systematic exploitation of the inductive method. Of course, the scientist has not an exclusive monopoly of this technique. Indeed, every one of us, almost from our first moment of consciousness, instinctively draws general conclusions from the few facts of his experience. Having once, or perhaps twice, found that fire is hot and burns, he will assume that every fire or indeed anything that looks like a fire is hot and will burn. But much of the inductive knowledge so built up is unsystematic, fragmentary, and often erroneous. The peculiarity of science is its insistent demand for accuracy as well as generality.

The problem of obtaining knowledge about the whole population from the study of a sample is, then, only a special case of induction, but it is a case of peculiar interest, for here the problem, being a precise numerical one, can be treated mathematically. It was Professor R. A. Fisher, then statistician to the Rothamstead Agricultural Research Station, who first saw the light in this difficult field, and gave a solution of the problem for certain special cases. His work has given us a rule or formula for making definite statements about the general population on the basis of a sample of that population. The rule can be so modified that the statements possess any required degree of reliability—that is to say, so that any pre-determined percentage of them are inevitably correct. Of course, the higher the reliability demanded the vaguer the statements necessarily become.

The great significance of this work, apart from its special importance as a fundamental advance in the theory and practice of statistics, lies in the fact that it sheds a flood of light on scientific method and the nature of scientific knowledge in general. This clear-cut, concrete, numerical problem illustrates exactly the objects for which in science we are always striving.

One point calls for a short explanation. We have remarked that in ordinary physical experiments the chief errors which occur are errors of observation and measurement, whereas when we deal with biological problems we at once encounter a new source of error—the error of sampling. But it should not be forgotten that errors of observation and measurement still persist in biology, and are often, in fact, quite large as compared with those met with in most physical problems. The point is that we have a sampling error in addition. These two types of errors will combine with each other to decrease the content or reliability, or both, of the final result. Both can be reduced by the expenditure of time and money, by care in the design of the experiment, and by thought and skill in interpreting the results. The sampling error requires a treatment which is different in detail but not fundamentally new.

So far we have been discussing populations as aggregates of individuals. Now a human population is characterized by quite a large number of important features. Some refer to the physical build of the individuals, the average height, average weight, etc.; and there is another group of characters which is of great importance: rates of various kinds, such as the birth-rate or death-rate. It is easy to appreciate that, from a sociological or anthropological point of view, these somewhat abstract population characters are far more important than any particular observations referring only to a relatively small number of individuals. With their help we can say something about *all* the individuals in the population. And these population indices have another important property: they are, in general, much more stable than individual characteristics. For example, it is extremely unlikely that the birth-rates, or death-rates, for England and Wales will be very different during the next twelve months from what they were last year. Now, it is quite clear that we cannot, in general, predict who will die or who will bear children. We cannot distinguish between the individuals; we can only say how many of them will behave in a particular way and how many will not. As

individuals we are relatively free, as a community we are, to a very much greater extent, under the rule of a predestined fate. Almost inevitably, at least five thousand people will die next year in Great Britain as the result of road accidents. But, although certain of our acquaintances may seem more likely than others to be numbered amongst these unfortunates, we cannot prophesy with certainty what will be the fate of any single person.

This relative permanence of population characters, as distinct from those of individuals, gives them a special interest and significance. Further, it confers upon the population as a whole a kind of reality as a separate entity, composed of, but in a sense distinct from, the individuals in it. We can, in fact, regard the population as a unit characterized by certain features or "parameters". It grows or contracts according to its birth-rate and death-rate. It is like a gas composed of a large number of separate molecules: these molecules as individuals are outside our direct experience, but collectively they are responsible for the pressure, density, and temperature of the gas. And just as we can learn much of value about the gas by treating it as a continuous fluid, completely neglecting the individual molecules, so we can study populations as entities in themselves.

Though the study of populations is still in its infancy, yet in some ways it is essentially simpler than the study of individuals. The relation between the two is analogous to that between molecular physics and the study of the properties of matter in bulk. Physical and chemical science had to work at the latter for over three hundred years before it was in a position to tackle the former. If men were themselves the size of molecules, things might have been different. Similarly, if we were supermen to whom a thousand years were as one day and the whole world a speck of dust, the study of biology would doubtless have begun with populations in the mass—just as the bacteriologist began the study of microbes by working, not with single cells, but with whole colonies of germs

growing together in bulk. Only after much trouble and travail would it have dawned on us that individuals did exist, and that the population was in reality an aggregate of individuals. Much depends on the scale and the perspective.

But, it may be urged, is not this idea of a population as an independent entity rather an unreal abstraction, an artificial creation postulated simply for our convenience? This cannot be denied, but it is equally true of many other scientific concepts. A solid is in reality largely empty space; a fluid is not a continuous, uniform medium. Science, like common sense, is essentially empiric in her methods. Simplifying assumptions have always to be made, and she seizes upon whatever gives promise of working. A complete description even of a drop of water would be so complicated as to be incomprehensible and useless. The important thing is to seize upon the essential and universal features of the object in question. Common sense and intuition must be used, but again only as a means to an end. Once the important features have been guessed, a simplified model can be constructed, its behaviour can be worked out, and definite predictions made. If the results so deduced agree with the properties of the original object, even approximately, then we feel more confident that we are on the right lines and that our guess has been a good one. Discrepancies may suggest modifications and refinements, which again will be tested by experiment and observation. And so the scientific framework of knowledge is slowly and often painfully constructed, and the scaffoldings of bad guesses and provisional hypotheses are, one by one, discarded and forgotten.

But, at the best, the scientist's world is to a large extent an ideal world full of unrealities, or, we might say, full of half-truths; though we hope at least they are the important halves—that they contain the essential points. And so, although populations are undeniably only aggregates of individuals, their characters do prove to be important, and the science of populations is an essential section of biological knowledge.

A warning, however, is necessary. Population characteristics are extremely useful abstractions, but it must always be remembered that they give us statistical information only, and that they need not apply to any specific individual. It is an extremely common weakness of the human mind to overlook this distinction, and especially is this so in relation to human populations. Someone proves or imagines he has proved, let us suppose, that negroes are inferior in ability, on the average, to Europeans. This is a statistical conclusion, and does not necessarily apply to negroes and Europeans individually. And yet on the strength of it many a European would feel justified in assuming personally a superior attitude towards some particular negro who might in fact be much his superior.

A similar fallacy lies at the base of most aristocratic theories of politics. It is true, on the average, that gifted parents have gifted children. Ability, like physical stature, is in some measure a heritable character; but this fact is in itself no justification for the existence of a hereditary governing class or privileged caste. Nevertheless, it is not infrequently advanced as an excuse for the gross educational and social inequalities which are so obvious a feature of the world to-day. Thus, grave injustice may result from the failure to realize just what an average really is, and to remember that individuals in a population may vary widely from the average or mean. Proper appreciation of the true significance of statistical ideas is not only of academic, but also of practical importance.

Our discussion of the methods and aims of modern science has shown us that in spite of much diversity in the objects studied, there is a very real uniformity as far as the underlying principles are concerned. The purpose is to formulate statements of fact or, we might say, to draw a picture of nature, with maximum content and of maximum reliability. This holds whether the methods employed are qualitative or quantitative, whether the subject of study be inorganic nature or populations of living beings. Truth is commonly thought

of as the goal of science. That it is very important cannot be denied, but, as we have seen, truth alone is not enough. The statements we make, the conclusions we come to, must have precision and general applicability as well as truth. When the resources available are limited we must, in general, make our choice between content and reliability. With increased expenditure of time and labour it is usually possible to increase both factors. It is tempting to assume that with indefinitely large resources we could arrive at statements always true and completely precise and general: in other words, that absolute truth does exist. We shall inquire into this question in the next chapter, and in doing so shall find that Absolute Truth, like so many ideals of the past, turns out to be a will-o'-the-wisp.

VIGYAN MANDIR OFFICE

CHAPTER III

WHAT IS TRUTH?

SUPPOSE you are required to state your weight on some form which you happen to be filling up. If you have not been recently weighed, you will probably go to the nearest chemist's shop, mount a weighing machine, drop your penny into the slot, and read the weight off the dial. This you will consider sufficiently accurate for the purpose. You will be aware that the result so obtained is subject to certain errors, but these errors you will not usually stop to consider in detail. However, they are worth examining more carefully.

Of the errors which arise in the operation of weighing some are obviously referable to the weighing machine, but others arise from the nature of the object weighed. Thus, in finding your weight, it is likely that the greatest error would arise from the fact that you wear clothes. A little extra trouble would, of course, easily get rid of this error; you would either remove the clothing before weighing or else weigh it separately afterwards. You would not, however, even yet be in a position to state your weight with precision. Your body would probably be covered with a thin film of moisture which could in no way be considered part of the body itself. This film would therefore have to be removed or in some way allowed for. Clearly, too, the result would depend upon whether or not you had recently eaten a meal. You might decide to carry out the weighing after fasting for a certain length of time, but this would not remove all the difficulty, for the weight will be to some extent dependent upon the state of your finger-nails and the length of your hair. It becomes quite an arbitrary matter as to what set of conditions is chosen.

In fact, the notion of the weight of a living body, though quite real when only an approximate value is in question,

becomes less and less definite as we try to make it more and more precise. There is attached to it a degree of uncertainty which, though it may to some extent be reduced by precise specification, would appear to be an essential feature of the measurements. A little consideration shows that this type of uncertainty is common to practically all biological observations. The temperature of an animal, its length, its weight, or the weight of one of its organs, the volume of its blood: all these quantities, though quite real in an approximate sense, lose their definition whenever we attempt to determine them with high precision. Obviously the same is also true of many quantities related to inorganic objects, for example, the diameter of the earth, the height of a mountain, the length of a river. In fact, the difficulty is rather to find measurable quantities which are free from ambiguities of this kind. However, before pursuing this line further, we shall consider the other element in the process of weighing, namely, the measuring instrument, in this case the weighing machine.

The errors which this introduces into the result fall into two classes. The first consists of what may be called systematic errors: errors such as may result from the scale on the machine being wrongly marked, and which are therefore not eliminated by repetition of the measurement. Errors of this kind, though important in practice, need not detain us here, for they can be eliminated by removing the object from the machine and replacing it by standard weights of various sizes, thus in effect recalibrating the machine. The same considerations would hold if the balance were of the ordinary lever type. After being balanced by means of suitable weights the object could be removed and replaced by standard weights sufficient to establish balance again. In either case the essential process is to compare two objects, and the only property of the weighing machine that matters is its sensitivity to small differences.

It is here that the second class of errors comes in. This class consists of the random or chance errors resulting from undetermined or uncontrolled causes such as small fluctuations

of temperature, strong draughts of air or films of moisture. The effect of these factors is to cause slightly different results to be obtained when the same two weights are compared on different occasions under apparently the same conditions. Closely associated is the question of sensitiveness of the balance. Assuming that the reading is made by looking at a pointer, we perceive that however accurate our eyesight or however much the pointer may be magnified, no significance can be attached to variations in the pointer readings unless these are larger in size than those resulting from the random errors. Thus, if the random errors cause variations in the pointer reading of about one scale division backwards and forwards when the same weight is employed on different occasions, and if one pound additional weight causes the pointer to move approximately sixteen divisions, then the balance will not detect, in a single experiment, differences less than one or two ounces. To increase the accuracy of the balance, say fivefold, we could either increase the sensitivity so that one pound corresponded to eighty divisions, leaving the extent of the random fluctuations unchanged, or we might leave the sensitivity unaltered, and take measures to reduce the random fluctuations to a fifth. The accuracy, in fact, depends on the sensitivity of the instrument relative to the random variations produced by uncontrolled disturbances.

It is worth noticing that, with a balance of a given type, the degree of accuracy attainable depends on the time available to carry out the observation. After the weight is put on, the pointer usually swings about its mean position and so, to ascertain this position accurately, it is necessary to allow time for two or three swings. Now we have seen that the accuracy depends on the sensitiveness relative to the random fluctuations of the pointer. If we imagine the latter to be kept constant, we may increase the sensitiveness—as, for example, by raising the centre of gravity of the beam by means of a suitable adjustment. In this case the time of swing will become longer, and so the increased accuracy will necessitate more

time for the weighing. On the other hand, we may keep the sensitiveness constant and reduce the random error by carrying out a number of weighings and taking the mean of the result. Again we purchase accuracy at the expense of time. With a given type of balance and a given amount of time there is a definite limit to the accuracy obtainable.

Thus, in relation to the weight of a biological object, such as a human body or the organ of an animal, there are two main sources of uncertainty, the lack of precise definition of the object in question and the failure of the measuring instrument to give exact results. Of course, there is no necessary connexion between these two factors. In particular instances the one might be of much greater importance than the other. If now we have the job of weighing large numbers of men, or even the same man over and over again, on a measuring machine of which we do not know the accuracy, then it will clearly be difficult to decide whether the variations in our results are due to the limitations of the machine or to a certain indefiniteness in the object being weighed. For example, some of the men might happen to be weighed before breakfast and some after. Under these circumstances, we shall only be able to ascribe weights to the men with an uncertainty determined by the variations in our actual observations. It might all be due to the error of the instrument, but we should not be justified in definitely assuming this to be so.

If we pass from living to inanimate objects the uncertainty of definition still remains, but in the simplest cases, *e.g.* the weight or volume of a billiard ball, this may be reduced by careful specification apparently to an indefinitely small quantity. Similarly, by refinements of methods and the expenditure of time on the measurement, the accuracy of the observation may be made greater and greater. It seems natural to conclude that it could be made infinitely great provided that unlimited resources were available.

However, it does not always follow that what can be done successfully up to a point can be continued indefinitely with

equal success. Take, for example, the process of dividing into two. We may divide a quart of water into two pints and each pint into two half-pints, but if we go on dividing it up long enough we shall ultimately come to a molecule of water, and if we divide that into two, the product will be water no longer. Water, in fact, is not really continuous and uniform, though at first sight it looks as if it were.

Now, modern physics has found that something similar happens in relation to errors of measurement. There would appear, in a certain sense, to be a definite limit to the accuracy with which a particular object can be observed; this limit is of a rather peculiar kind and is best illustrated by a simple example.

If we imagine an electron as like a very small billiard ball, we are naturally inclined to think of it as having a position in space and a velocity. In order to ascertain these, it is necessary to employ some means for getting in touch with the particle. A method of communication must be provided between the experimenter and the experimental object, and the simplest and most delicate instrument to employ is a ray of light. We send out a ray in the direction of the particle; and, if it is reflected back, we may deduce from it the position of the particle, by employing a microscope of appropriate design.

Now, it is a fundamental principle of optical instruments that high accuracy of location is possible only when light of short wave-length, that is of high frequency, is employed. Consequently if we are to locate the electron with extreme exactness it will be necessary to use light of very short wave-length. We know that light is atomic just as matter is; it exists in bundles or packets each of a particular size according to the frequency. Furthermore, every packet or quantum of light has a certain momentum, and so when the light collides with the electron it necessarily imparts to it momentum and velocity just as one billiard ball does when it collides with another. But light of high frequency is composed of quanta of very large momentum, and so the electron is likely to

undergo a large change of velocity. Furthermore—and this is the essential point—the exact magnitude of this change of velocity cannot be calculated from the observable quantities. The uncertainty in the velocity therefore cannot be made less than that due to one quantum of the light we have chosen to use. The result is that the location of the particle in space can be determined accurately only at the expense of imparting an unknown change of velocity. The greater the accuracy of location, the greater the magnitude of this unknown change is likely to be.

In an analogous way it is found that any observation by means of which the velocity of an electron is accurately determined results in a degree of uncertainty being introduced in respect of its position. Repetition of the observations does not help, for each observation imparts a disturbance to the particle, and this offsets the information which the observation gives us. The result is that no experimental observation whatever will tell us with precision both the position and velocity of an electron at some particular instant. The more accurately we know the one the greater our ignorance of the other. Once more it is the case of the butter and the jam; we can have a little of both, but the more we have of the one, the less there will be of the other.

This great principle of uncertainty or indeterminacy, enunciated in 1927 by the famous German physicist Heisenberg (who was only twenty-five years old at the time!), appears to be fundamental in the physical universe. It is closely connected with another conclusion of modern physics, namely, that the results which we can calculate with precision for any physical system are statistical results. Thus, if we have a large number of atoms or electrons, all identical with each other, within a box, the laws of physics as at present known allow us to calculate what proportion will be doing one thing and what proportion another at any particular instant; we cannot predict with certainty what any individual atom or electron will be doing. If the experiment involves not a large

number of electrons but only one, then the equations which physical theory provides must be interpreted in the sense of probabilities of the electron doing *a*, *b*, or *c*. This means that if we repeat the experiment a large number of times, our theory tells us in what proportion of cases we shall obtain the results *a*, *b*, or *c* respectively, but we are never certain what the result will be in any particular experiment. The fact that physical theory in general gives no definite result for particular experiments may appear at first sight very surprising and unsatisfactory, but a little reflection shows that it is the natural consequence of the uncertainty principle; for, according to the latter, the initial conditions of the experiment can never be completely known in the ordinary, mechanical sense, and so the result is necessarily vague and unpredictable.

It is worth while noting the curious analogy between this result of modern physics and the conclusions we reached in the last chapter whilst discussing the characters of populations as compared to those of individuals. Just as it is impossible to predict with certainty what any particular individual will do, so we cannot predict the behaviour of individual atoms or electrons. On the other hand, the behaviour of whole populations is a much more definitely predictable matter. We can often say with considerable accuracy what proportion will die of cancer and what proportion will commit suicide. It becomes evident that the reason why the laws of inorganic nature are so much more exact than those relating to biological phenomena is that the former usually refer to entities which are themselves really populations of enormous size. The ordinary laws of electricity and magnetism, of gravitation and planetary motion, are usually applied to groups of electrons or atoms involving perhaps 10^{24} in number. With these high numbers the uncertainty or indeterminacy still exists, but it has become very small in proportion to the whole. The uncertainty in the motion of the centre of gravity of the earth in its journey round the sun is finite but extremely minute and no doubt beyond all possibility of experimental observation. Two pieces

of pure copper behave in apparently the same fashion when subjected to the same conditions because the number of atoms in one gramme of copper is about 10^{22}. If we could obtain populations of flies or rabbits comparable to this in numbers, they would also behave, in the mass, with very constant uniformity. Even the relatively very small populations of which we have experience already show a degree of predetermination in their behaviour quite foreign to the individual. We have already referred to an example of this in the case of road fatalities; many other cases readily occur to the mind.

The analogy between the living and the non-living world has another aspect of some significance. We have seen that every observation made on the electron communicates to it a disturbance, of which the magnitude cannot be definitely calculated. The mere act of observation alters that which is observed. The same difficulty is met with in connexion with biological and especially psychological observations on animals or human beings. In performing a mental test the individual learns something. Afterwards he is no longer exactly the same as he was before. Successive tests may give different results because the subject of the test is changing. Of course, devices can be employed to overcome this trouble, but these all involve the use of a number of individuals, and the larger the number, the more effective they are. Just as in the case of atoms and electrons, the laws of psychology are, in the last resort, statistical laws.

But, it may be urged, these are, after all, only analogies, and analogies possibly of a rather superficial kind. It may be replied that our understanding of the ultimate constituents of the universe around us must perforce depend on analogy. We can describe the behaviour of things in abstract terms, by means of mathematical symbols. With the help of these we are enabled to make our statements of maximum content and of maximum reliability. But these statements remain strange and meaningless to us unless we can interpret them in some way in terms of objects with which we are familiar. Now, it

happens that we have no direct appreciation of electrons in the ordinary sense. They are below the point zero in our scale of magnitudes, and our senses acquaint us directly only with objects of sizes between 20 and 40. To comprehend things below and above this range of magnitudes at all, we must think of them in terms of things which lie within this range. The older physicists, working on a basis of Newtonian dynamics, got much satisfaction by devising models of atoms based on billiard balls, vortices, magnets, and what not. All such attempts proved themselves to be unsatisfactory. The failure resulted from the fact that the mechanical systems involved were altogether of the wrong type: they did the wrong sort of things. Our grandfathers assumed that the electron could be specified in respect of its position and its velocity just like a planet and that its future behaviour could then be calculated in the same precise way. This is all wrong. The analogies employed, even as analogies, were not really sound ones.

All attempts to represent the simple in terms of the more complex, the fundamental entities in terms of the final product, must necessarily fail to some extent. It is like trying to describe bricks in terms of houses. To satisfy our natural craving for some concrete picture of the realities which lie behind the highly abstract statements of modern physical science, we are forced to picture them in terms of things of which we have immediate knowledge. We have some immediate knowledge of our own thought and volition, of choice and spontaneous decision. These internal perceptions are quite as real as the external ones. If we want to depict an atom, it is just as legitimate to incorporate the one as the other. In neither case is there any real explanation. In as far as this is to be found at all, we must expect to find it in the highly abstract mathematical equations and the other generalized statements which form the essential basis of quantum mechanics. But when we want insight into the nature of the processes involved, when we want to feel that in some small measure we understand them, it is just as legitimate to picture

them in terms of spontaneity and choice as in terms of elastic balls and compass needles. It is all a question as to which works best, and the biological notions are sometimes helpful when the physical ones completely fail.

It is difficult in any discussion of the relation between modern physics and biology to avoid some reference to the question of the existence of free-will. We have just seen that from the point of view of pictorial representation the atom and electron may conveniently be thought of as exercising a certain degree of choice. Their behaviour is determined only in the statistical sense. This is a description of the fundamental entities in terms of a property characteristic of living things. But it is possible to reverse the process and inquire what light is shed by modern physics on the general nature of living organisms.

The dynamics developed by Newton and his successors asserted quite definitely that if we knew the position and velocity of every particle in any mechanical system at some particular instant of time and also all the forces acting on those particles, we could calculate the behaviour of the system at all future times. Its history would be absolutely determined.

The question at once arose as to whether living organisms were systems to which this principle applied, whether, in fact, the behaviour of every animal—worm, mouse, or man—would be completely predictable, and therefore predetermined, to a being sufficiently omniscient and able to perform the necessary calculations. To many minds an affirmative answer to this question appeared obviously ridiculous. They were deeply impressed by the essential difference in the behaviour of animals, both superficially and when studied more profoundly, as compared with that of even the most complicated inorganic systems. They particularly emphasized the direct appreciation of individual freedom of choice which we all experience and which appears to possess as much reality as can be attributed to material objects. They therefore concluded that man and the lower animals possess attributes not found in inorganic

nature and resulting in an essential unpredictability of behaviour. Others preferred to regard all failures to predict behaviour as simply the result of incomplete knowledge of the forces at work. Everyone is agreed, they pointed out, that the wind, which apparently "bloweth where it listeth", is actually a predictable phenomenon given a sufficient knowledge of meteorology. The behaviour of some living organisms is, in fact, more easily predicted than that of the wind; man, they argued, merely presents in its acutest form a difficulty found in all complicated systems.

Thus there came about the controversy between mechanism and vitalism; between predestination and free-will. It became necessary either to agree that nature was in some measure a duality composed partly of living, partly of dead matter; or else to consider that all our direct consciousness of volition and decision is illusory. Both alternatives were profoundly unsatisfactory.

But we now see that the whole basis of the argument was unsound. The Newtonian dynamics just does not hold. We have seen that it is impossible to specify both the position and velocity of a particle at any one instant of time. It is true that when the particle is a large one, like a planet or even a billiard ball, both position and velocity may be specified with very great accuracy, but still not with *absolute* precision. Thus, even if the Newtonian laws held, we could not predict exactly the state of a system at any future time, for we could never know its initial state with sufficient exactitude. In fact, the whole idea of complete predictability, even in inorganic nature, proves to be quite illusory. Accurate prediction is impossible because at no instant of time is a complete specification in the Newtonian sense feasible, and not because a "vital" force is constantly interfering.

It is not difficult to design purely mechanical systems which, if actually constructed, would exhibit unpredictability of behaviour in a very real and obvious sense. Suppose, for example, we had a stream of electrons shot from some source

through a very minute hole. If an electron passing through a hole behaved like a billiard ball passing through a proportionately wider aperture, it would, of course, go on in a straight line and its course would be perfectly predictable if the aperture were made sufficiently small. But modern quantum mechanics shows that electrons do not behave like this; though not under any force in the ordinary sense they would tend to be deviated from their course by the mere fact of passing through the hole and would emerge in different directions. The degree of this scattering would be the greater, the smaller the diameter of the hole. As far as is known it would be impossible to predict the path of any individual electron after passing through the hole; we can calculate only the distributions of the paths in a statistical sense. Let us suppose now that we have a number of Geiger counters put in various places on the far side of the hole. (A Geiger counter is a vacuum tube containing two electrodes across which an electric potential is applied, and it is so constructed that if an electron passes through it an electric discharge takes place.) Each counter may be connected to a system of valves, condensers, etc., so arranged as to magnify the electric disturbance produced by the transit of the electron, and the resulting impulse can then be employed to initiate some quite obvious effect (Fig. 8). Thus one counter when activated might switch off your wireless set; another might launch the latest liner; whilst a third might blow up the House of Commons. Assuming then that such a system was constructed and that one or two electrons were allowed to pass through the hole, we could not foretell whether one or other or none of these various effects would be produced. This would be true, however much care was taken to control the path of the electron before it passed through the hole. Evidently then, unpredictability is not limited to atomic phenomena alone, but with suitable arrangements it may be made manifest on the grand scale. In the random assortment of atoms and molecules constituting a gas or liquid, and even in the simple type of structures called

crystals, these unpredictable effects tend, in the aggregate, to neutralize each other and to produce no lasting or obvious result. But with an arrangement of the kind we have imagined above, these chance occurrences may be made to bring about important and impressive events.

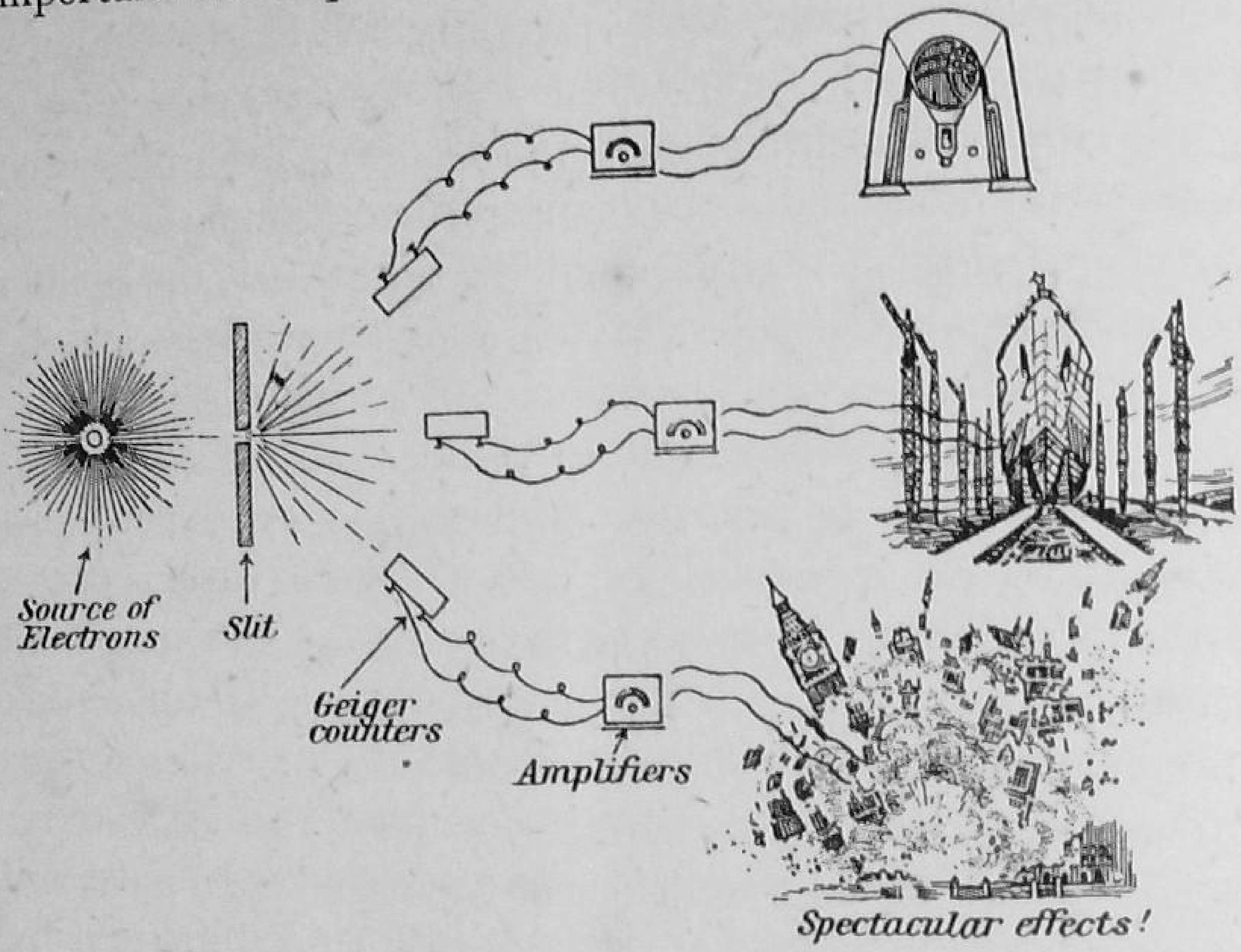

FIG. 8.—Showing how the uncertainty principle could be made manifest on the grand scale.

So far we have laid emphasis on the point that the behaviour of an electron is unpredictable. This lack of predictability is admitted by all, but the question at once arises as to whether it is an essential property of the electron, or merely a consequence of the limited powers of the instruments at our disposal for observing it. We know of nothing finer than a ray of light for this purpose, but it may be that some more delicate tool does exist, and that if we knew of it we could determine simultaneously both the position and velocity of an electron. If the position and velocity could be simultaneously measured by some method, the future behaviour of the electron might then be predictable with certainty. But there is at present no hint whatever of the existence of any such refined tool.

Neither view as to the origin of the unpredictability of natural phenomena—whether it is an essential feature of all material systems or merely a consequence of our limited powers of investigating them—can be disproved; our choice will depend on which seems to be more fruitful and convenient in practice.

There is, however, a general principle which has proved of much value in modern physics, to the effect that it is dangerous and undesirable to attribute reality to that which cannot be observed. It does not follow, of course, that unobservable quantities are *necessarily* unreal and fictitious; the trouble is, it is all too easy to assume, perhaps quite unconsciously, the definite existence of some quantity or quantities—such as precise location and velocity—and to forget that these have never been directly observed and for all we know may not actually exist. We might emphasize that we cannot actually disprove this assumption—the hypothetical objects *may* exist for all we know—but this does not really take us very far. By the same argument we should have to allow the possibility of the existence of a Man in the Moon. Experimental observation cannot and possibly never could, disprove his existence; for even though we possessed the finest optical instruments he might live on the other side, the side we never see. Unless, therefore, there is some cogent reason for assuming that our fundamental entities such as protons and electrons must necessarily possess both position and velocity in a precise sense, it seems reasonable, and, on the whole, preferable, not to do so.

It can of course be argued that there is something profoundly unsatisfactory in leaving the ultimate laws of nature in this non-deterministic, statistical form. But is this really so? Is this objection not fundamentally of the same type as that which was raised against the idea that the earth went round the sun or that space was not Euclidean? Obviously the sun went round the earth; obviously space is flat, not curved. But the obvious is not always true. Now, the ordinary non-living systems with which we deal in daily life seem in the same

obvious way, completely predictable in their behaviour, or would be if we took trouble enough to study them sufficiently. This vague but deeply rooted impression of the predictability in behaviour of inorganic matter, which we all form from our everyday experience, has been immensely strengthened and apparently scientifically justified by the development of dynamics through the genius of Newton and the work of his successors. It is, for this reason, difficult to examine the situation in an unprejudiced frame of mind. But if we realize that science is essentially descriptive, it will be appreciated that we must fit our descriptions to the objects observed and the statistical laws of modern physics seem to furnish the best available description so far devised. They have at least as much claim to be considered fundamental as any other laws.

The view that physical systems are essentially unpredictable has the great advantage that it seems to avoid altogether the dilemma between Mechanism and Vitalism. The difficulty turns out to have been a fictitious one, produced as the result of making assumptions for which there was absolutely no warrant. The assumptions may have been true—you cannot absolutely disprove them—and in that case the dilemma still exists; but we are putting ourselves to quite unnecessary trouble if we worry about the consequences of unwarranted hypotheses. It seems much more fruitful to adopt the newer point of view—at least until some discovery is made which renders it untenable. We may therefore work on the assumption that the whole of reality, living and non-living alike, is essentially a unity, all of which, in the ultimate analysis, can be described in the same terms and by the same laws. It would be misleading to call this point of view either Mechanistic or Vitalistic; but it does seem to preserve the essential advantages of both these philosophies.

Let us look at the matter from a somewhat different angle. Can we really observe an electron? If it happens to pass through a Geiger counter we are made aware of the fact by the movement of a pointer or by the noise in a loud-speaker.

These effects are produced by the electron through the somewhat complicated electrical system of valves, conductors, and condensers which magnify the initial disturbance. Sometimes the electron is detected as the result of its producing a spot or line on a photographic plate. In the extreme case, one might imagine that it was illuminated and viewed by the eye through a suitable microscope. Here a disturbance would ultimately be produced in the optic nerve of the observer. In all cases the data which are immediately observable consist of effects of a gross kind, physical or chemical reactions involving millions of atoms or molecules. Thus scientific observations in the ultimate analysis refer to gross observable effects or objects. In order to correlate these it is found convenient to assume the existence of a large number of electrons, protons, quanta, and suchlike, which taken together form, as it were, a delicate network connecting up the various gross effects which are directly observed. In this sense these fundamental entities are convenient hypotheses, but it greatly aids us, in thinking about these matters, to conceive of them as small particles or trains of waves, or as both. It is, however, the large-scale objects which are really observed.

Now the relationship between two such objects may be of a relatively simple type. There may be no highly complicated structure, or, if there is, it may not be relevant. Such connexions may be capable of expression without any reference at all to the individual electrons and quanta. Simple relationships of this kind underlie the phenomena which were dealt with by the older classical physics. On the other hand, the connexions may be complicated and highly critical. The underlying structures, represented in terms of electrons, protons, and quanta cannot be dispensed with if an intelligible description of these more complicated relationships is to be achieved. We are then dealing with the phenomena which have necessitated the development of the new physics: the connexions are now more subtle and not always so precise as in the simpler cases of the first type. Of all the complicated

structures and complex relationships, those existing in the living cell are probably the most extreme examples. Thus, in living beings we have phenomena altogether beyond descriptions of the older type. The climax would seem to be reached in the nerve cells of the brain, and so, in the mental activity of the higher animals and of man, we seem to reach the greatest degree of unpredictability in the old mechanical sense.

But all this is somewhat general and abstract. The vague outline of the universe around us which this picture affords must be filled in if it is to be a serviceable and satisfactory interpretation of our everyday experience. We want some concrete and comprehensible notion as to how a bacterium, a frog, or a man's brain actually works. They are all composed, like a lump of iron or stone, of protons and electrons and the other elementary particles. And yet they all behave so very differently. Too great detail in our picture is neither possible nor desirable. It would merely confuse us—the wood could not be seen for the trees. We want just that amount of detail which allows us here and there to make contact with real objects, but never so much as to be merely distracting. And so, between the Scylla of vagueness and the Charybdis of a plethora of trivial facts, we shall endeavour to steer our way in this voyage of survey.

CHAPTER IV

ATOMIC BRICKS AND MORTAR

IF we set out to discover how some mechanism works, our first concern is to find out how it is constructed. If we do not know the nature of the component parts of a motor-car engine, what they do, and how they are connected to each other, we cannot hope to understand how the engine is able to produce mechanical energy as the result of burning petrol. In the same way, in order to elucidate the behaviour of living bodies it is necessary to find out all we can about their structure. The more exact and complete this knowledge, the easier it becomes to explain functional activity in precise and unambiguous terms.

There are, of course, different levels on which explanations of structure may be given. In the case of the motor-car, for instance, we may take the coil and the carburettor as units capable of doing certain things, and for the time being neglect the question as to how these units work. We need only know that the coil causes a spark to be produced in the cylinder at the appropriate instant; we leave aside the question as to how this spark is actually produced. In this way we are able to give a description of how the engine works as a whole. We realize that this knowledge is incomplete and that the next thing to do is to study the structure of the coil; but however imperfect, the explanation of the whole in terms of its parts constitutes a distinct advance and is the first step towards a more complete explanation.

It is the same with living structures. No advance towards an explanation of their working can be expected until they have been closely studied from the point of view of anatomy. This science was one of the earliest of the biological sciences to develop, and through it the physical relationships of the

various organs in the body to each other were made clear. The discovery of the microscope made it possible to extend our knowledge of structure so as to include details too minute to be observed by the naked eye.

During the course of the nineteenth century this "histological" knowledge of living structure was immensely extended by the development of the technique of section cutting and the staining of tissues by means of suitable dyestuffs. For a histologist the unit is the cell. Sometimes, it is true, he is able to see within the cell various particles and granules and even more detailed structures, but he is never quite certain as to how far these really existed in the cell in its living state before he began to treat it with his highly specialized and often quite drastic methods. In any case, he almost invariably fails to give any explanation of the function of the cell in terms of these structures. Thus it may be said that, if we approach the problem of structure by the method of direct observation we begin to reach the limit of our resources when we get down to about the size of the cell, which is in the neighbourhood of point 14 on our scale (p. 9; see also Plates I and VII).

Fortunately another kind of approach is available. This is, as it were, from below upwards. The bricks of which the cell is built are chemical molecules, and in order to understand the behaviour of these it is necessary to know their architecture; this means that we must first make a short digression about atoms, for these are key-units in the structure of all things, living and non-living alike.

It is now well over a hundred years since Dalton put forward the atomic theory, which has become the basis of the science of chemistry. In this theory the unit is the atom, and the large mass of facts discovered by the work of chemists is brought into an orderly system when interpreted in terms of these atoms. The chief property possessed by most atoms is the power of combining with other atoms to form new compounds. In terms of this theory in its early, simple form, the

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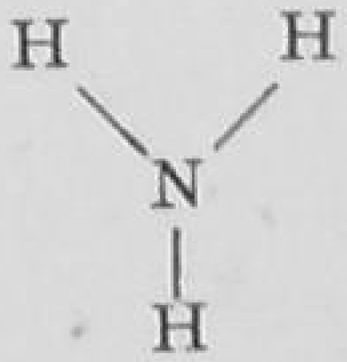
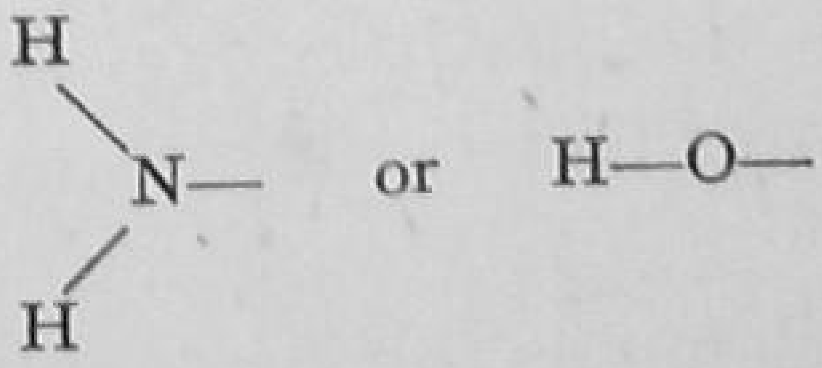
atom may conveniently be thought of as a sphere furnished with a number of hooks each representing one "valency". Certain types of atoms—those of hydrogen, sodium, and chlorine—have only one such hook; others, calcium, sulphur, and oxygen, two; nitrogen and phosphorus have three; carbon, four. A "bond" is formed between two atoms when one hook of one atom engages with one hook of the other—

Hydrogen Chloride.

It has been found very convenient to denote an atom by a simple symbol, usually the first letter of the name of the element—see Table I—and to denote the bonds by lines. A molecule of a compound may then be represented by a number of these symbols each denoting an atom joined by lines symbolizing the bonds. Thus a molecule of water is represented by H—O—H, ammonia by



These formulae illustrate an important principle which is quite fundamental in the theory, that in all stable molecules there are no free hooks left over; thus, for example, it is found impossible to isolate a substance,



With the help of this theory of molecular structure chemists found it possible to interpret a very large number of compounds in terms of atoms. These compounds include many

found in inorganic nature and in living bodies as well as an enormous number synthesized in their laboratories.

During the present century an advance has been made towards a description of nature in still more fundamental terms. The physicist discovered the proton and the electron; apparently the fundamental positive and negative units of electricity. The proton and electron carry charges equal in amount, though of course of opposite sign, and the combined work of physicists and chemists enables us to picture the atom as something like a miniature solar system with a central nucleus surrounded by a planetary system of electrons. We may, for present purposes, regard this nucleus as a highly condensed system of protons and electrons with an excess of the former. It is therefore always positively charged, but this charge varies according to the type of atom in question. Around this nucleus are disposed a number of electrons, just sufficient to render the atom as a whole electrically neutral. This number, which is naturally equal to the number of excess protons in the nucleus, determines the kind of atom in the chemical sense. Thus, if it is 1 the atom will be an atom of hydrogen; if it is 6, carbon; if 7, nitrogen; if 8, oxygen; if 17, chlorine. In other words, hydrogen, carbon, nitrogen, oxygen, and chlorine have 1, 6, 7, and 17 planetary electrons respectively. Now these electrons are arranged in shells. The fundamental idea is that the number of available places on each shell is limited. There cannot be more than 2 in the first, 8 each in the second and third, 18 in the fourth, and so on. Hydrogen and the inert gas helium, with 1 and 2 planetary electrons respectively, form the first group of elements, with only the first electron shell occupied; partly occupied in the case of hydrogen; fully in the case of helium (see Fig. 9).

In the next eight elements this first shell remains completely filled and the second shell is gradually completed, one electron at a time, as we pass along from lithium to the next inert gas neon. Thus carbon, which has a total of 6 electrons, has a

complete inner shell of 2 and a half-completed outer shell of 4. With the next eight elements, sodium to argon, the story is repeated, the inert gas argon having three complete shells (2, 8, and 8 electrons). It will be noticed that the inert gases —so named because of their reluctance to enter into chemical

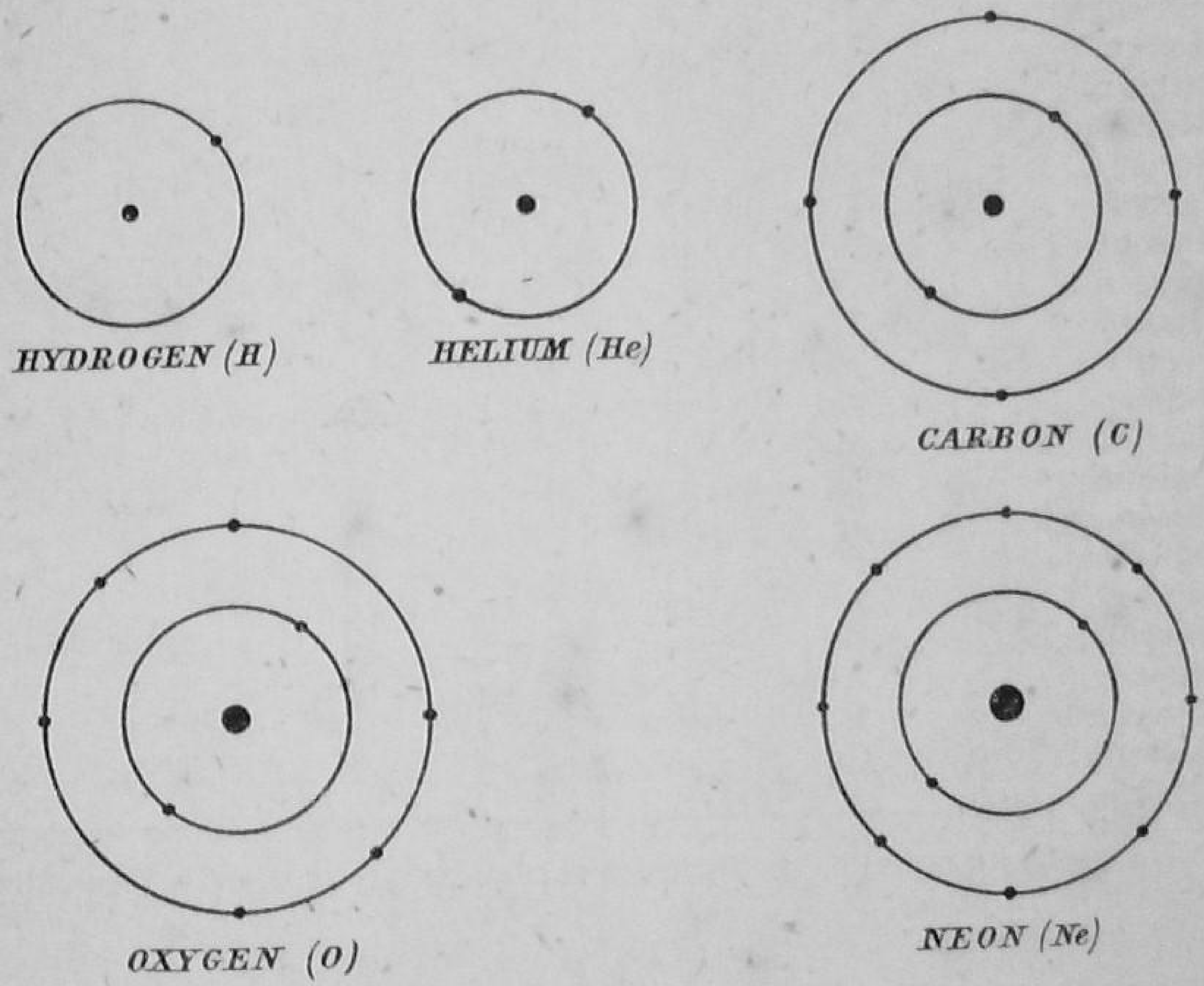


FIG. 9.—Diagrammatic picture of atomic structures. The large dots represent nuclei, the small ones electrons.

combination—are peculiar in their having complete outer shells. Here we have the clue to the whole of chemistry. Completed shells are stable ones which seem perfectly happy to remain as they are and show no desire for change. Incomplete shells, on the other hand, are uneasy and uncomfortable arrangements always in a state of unrest. Wherever possible the electrons will try to rearrange themselves in such a way that incomplete shells will no longer exist. It is this principle which underlies chemical combination and which dominates molecular structure.

TABLE I.—THE LIGHTER ELEMENTS AND THEIR ATOMIC STRUCTURE

Element	Symbol	Atomic Weight	Charge on Nucleus*	Electrons in			
				1st Shell	2nd Shell	3rd Shell	4th Shell
Hydrogen	H	1	1	1	—	—	—
Helium	He	4	2	2	—	—	—
Lithium	Li	6·9	3	2	1	—	—
Beryllium	Be	9	4	2	2	—	—
Boron	B	10·8	5	2	3	—	—
Carbon	C	12	6	2	4	—	—
Nitrogen	N	14	7	2	5	—	—
Oxygen	O	16	8	2	6	—	—
Fluorine	F	19	9	2	7	—	—
Neon	Ne	20·2	10	2	8	—	—
Sodium	Na	23	11	2	8	1	—
Magnesium	Mg	24·3	12	2	8	2	—
Aluminium	Al	27	13	2	8	3	—
Silicon	Si	28	14	2	8	4	—
Phosphorus	P	31	15	2	8	5	—
Sulphur	S	32	16	2	8	6	—
Chlorine	Cl	35·5	17	2	8	7	—
Argon	Ar	39·9	18	2	8	8	—
Potassium	K	39·1	19	2	8	8	1
Calcium	Ca	40·1	20	2	8	8	2

* Numerically equal to the number of planetary electrons (often called the atomic number).

Let us examine how this works out in practice. Suppose, for example, we have an atom of sodium and an atom of chlorine. It will be seen from Table I above that the sodium atom has an incomplete shell containing one electron and the chlorine an almost completed shell of seven electrons. Obviously, if a single electron is transferred from the sodium to the chlorine there will no longer be any incomplete shells. This transfer, of course, results in the sodium acquiring a positive charge and the chlorine a negative one. For convenience we speak of those charged atoms as ions. Being of opposite signs the sodium and chlorine ions attract each other and it is this electrical attraction which is to be interpreted as the bond in a simple compound like sodium chloride (common salt). A

crystal of sodium chloride really consists of a closely packed and regularly arranged aggregate of equal numbers of such positive and negative ions (Fig. 10). As each negative ion is surrounded by positive sodium ions and *vice versa*, it will be

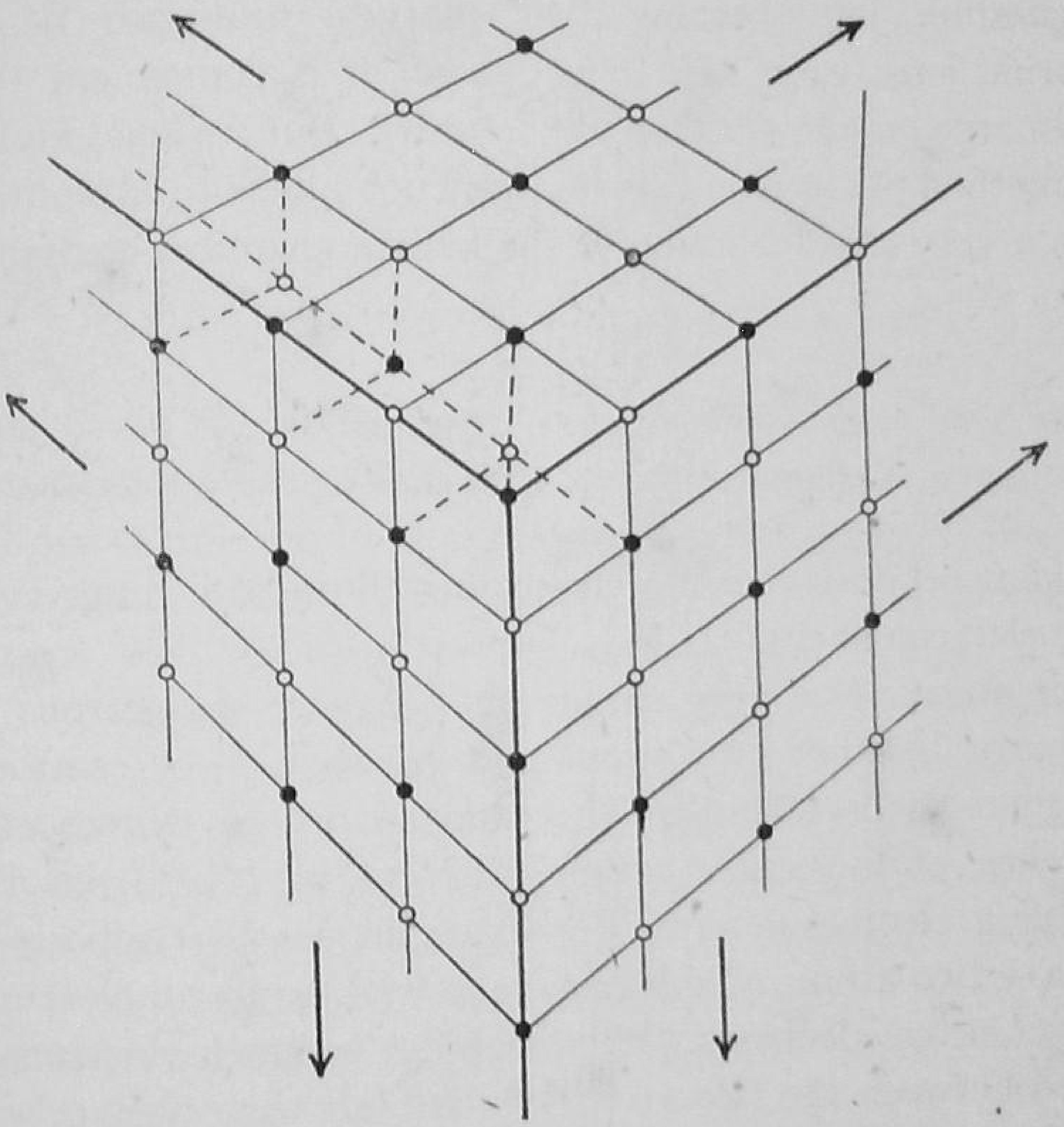


FIG. 10.—Illustrating the arrangement of atoms in a sodium chloride crystal

● = a positively charged sodium atom
○ = a negatively charged chlorine atom

Each sodium atom has six chlorine neighbours and every chlorine six sodium neighbours.

readily understood that the electrical forces holding the structure together reach quite considerable magnitudes, so that a crystal of sodium chloride is a hard, rigid structure.

This idea of *electrovalency*, as it is called, involving the formation of electrically charged ions, covers a number of

simple cases met with in inorganic chemistry. An atom of magnesium, for example, has two extra electrons. It cannot, therefore, react with one atom of chlorine, like sodium, but must react with two, giving up one electron to each. We thus obtain the salt magnesium chloride, containing a positive magnesium ion (bearing two charges) and two negative chlorine ions, each with one charge (it is convenient to use the charge on one electron as the unit). But we soon find that the method of electron transfer does not suffice to explain more than a very small fraction of the known chemical compounds.

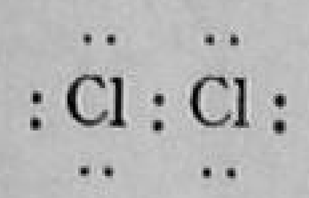


FIG. 11.—A chlorine molecule. The dots represent electrons.

By what other device can the atoms "liquidate" their incomplete electron shells?

The answer is a very simple one. A pair of electrons may be shared between two atoms and are then to be counted in the outer shells of both. This sharing process allows of the existence of molecules rather different in type from those involving electrovalency. For example, let us suppose that we have two atoms of chlorine, each with an incomplete outer shell of seven electrons. If two of the fourteen electrons are shared between the two atoms, we are left with twelve, which may be arranged six round the one and six round the other. This is represented diagrammatically in Fig. 11, in which, according to custom, only the outer electron ring of each atom is depicted, the inner (completed) rings being taken for granted. It will be seen that each atom has now a complete outer shell of eight electrons, namely, the two shared ones and six others. The whole structure constitutes a molecule of chlorine such as would be represented in the old notation by the formula Cl—Cl. The pair of shared electrons forms the bond or valency, which holds the atoms together.

There is one subsidiary rule which should be mentioned at

this point. Undue accumulation of free electric charges on any atom in a molecule leads in general to instability. Thus, charges of one unit or even of two are permissible, as in the cases of the sodium and magnesium ions mentioned above; but in the case of carbon tetrachloride, CCl_4, although the

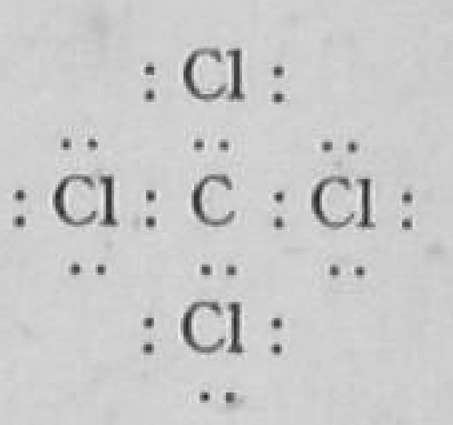
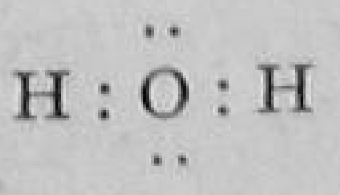


Fig. 12.—A molecule of carbon tetrachloride.

carbon could theoretically give up its four outer electrons to complete the outer shells of the four chlorine atoms, thus becoming a quadruply charged carbon ion, such an ion does not normally exist. It is found that the carbon shares its electrons with the chlorine atoms as shown in Fig. 12, the atoms of chlorine and carbon remaining electrically neutral. This sharing of electrons is a predominant feature of the compounds in which we are particularly interested, namely, the compounds of carbon, hydrogen, oxygen, and nitrogen; the electron shells are all complete, and usually the individual atoms in the molecule are electrically neutral.*

Let us now consider the formulae of water and ammonia in terms of electrons.

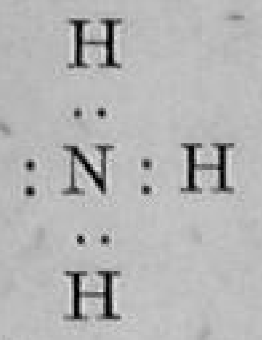
It will be readily seen that a molecule of water is appropriately represented by



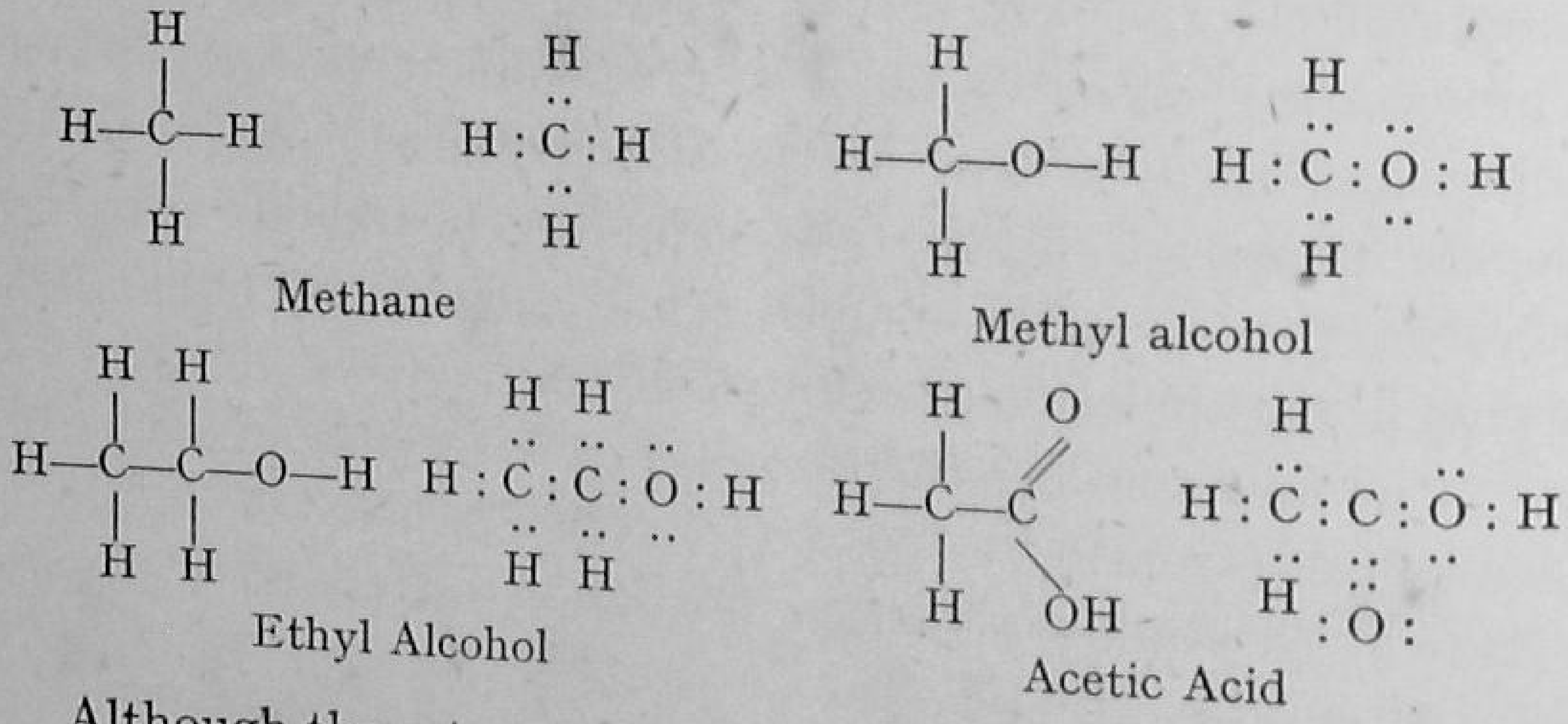
This formula satisfies all the conditions laid down above, for the oxygen atom is connected to each hydrogen by two electrons and is itself surrounded by eight, whilst the total number of electrons is correct, being made up of six originally

* Here, "neutrality" means that the charge on the nucleus is equal to the number of free unshared electrons plus half the number of shared electrons.

belonging to the oxygen together with one from each hydrogen. Similarly, the formula for ammonia is correctly represented as



If we compare these electronic formulae with the older formulae given above, it will be seen that each line representing a bond has been replaced by two dots each representing one electron. The new method of representation brings out the fact that certain atoms may also carry free or unshared electrons in their outer shells. It is of interest to write down the formulae of a few simple substances in each of the two ways. We therefore give the old and the new method of representing methane, the gas responsible for firedamp in mines; methyl alcohol, or wood spirits; ethyl alcohol, the chief cause of drunkenness; and acetic acid, the characteristic constituent of vinegar.



Methane   Methyl alcohol

Ethyl Alcohol   Acetic Acid

Although these two methods of representing chemical bonds are essentially equivalent to each other, the new one has certain distinct advantages. In the first place, it is logically more satisfactory, because it describes chemical phenomena in terms of particles or concepts recognized by physics as fundamental in the structure of things and deduced by this latter science on largely independent evidence. In the second place, it accommodates certain types of compounds and reactions not readily explained by the old basis; for example,

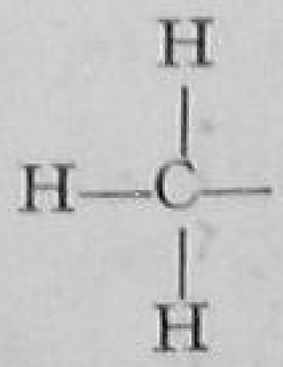
the fact that ammonia gas, NH_3, can combine with hydrochloric acid gas, HCl, to form a salt is now easily understood. All that happens is that a hydrogen ion breaks away from its partnership with chlorine and forms a new union by sharing the two free electrons of the ammonia molecule:

ammonia + hydrochloric acid → ammonium chloride

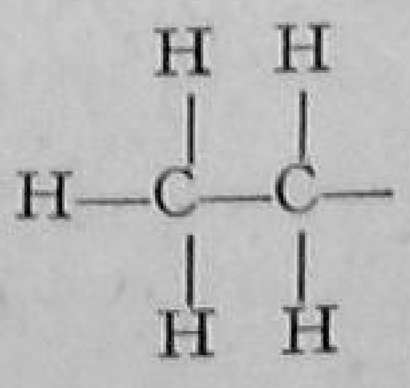
The result is the creation of a positively charged ammonium ion and a negatively charged chloride ion. These, taken in bulk, constitute a crystal of the salt we call ammonium chloride, just as an aggregate of sodium ions and chloride ions constitute a crystal of sodium chloride (see p. 35).

Thirdly, the electron interpretation of valency is found to explain the course of chemical reactions in a way which was quite beyond the powers of the old theory.

Both these methods of writing out formulae, however, suffer from one disadvantage—they take up too much room. In consequence, for ordinary purposes it is customary to use an abbreviated notation. We take as our unit not one atom but a group of atoms. These groups may be concisely denoted by a statement of the atoms they contain, the actual bonds being omitted where ambiguity does not thereby result. Thus, the group containing one carbon and three hydrogen atoms, represented by the full formula



is denoted by CH_3 and is called the methyl group; a group consisting of two carbon and five hydrogen atoms



is represented by C_2H_5 and is called the ethyl group. In this notation the four compounds pictured above are represented as follows: CH_4; CH_3OH; C_2H_5OH; and CH_3COOH.

This conception of the group as the unit has been of extreme value in the development of structural organic chemistry. The same groups are met with over and over again in all kinds of different compounds, and the important point is that the properties and behaviour of any group are to a large extent independent of the rest of the molecule to which it is connected. Thus, if we know the properties of these groups, we know a great deal about the properties of any compound which

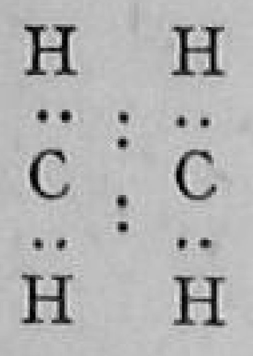


FIG. 13.—Ethylene.

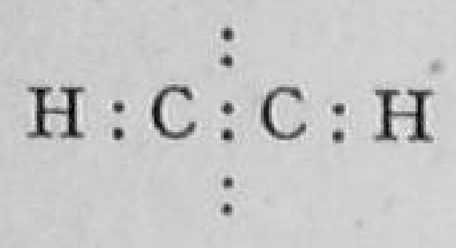


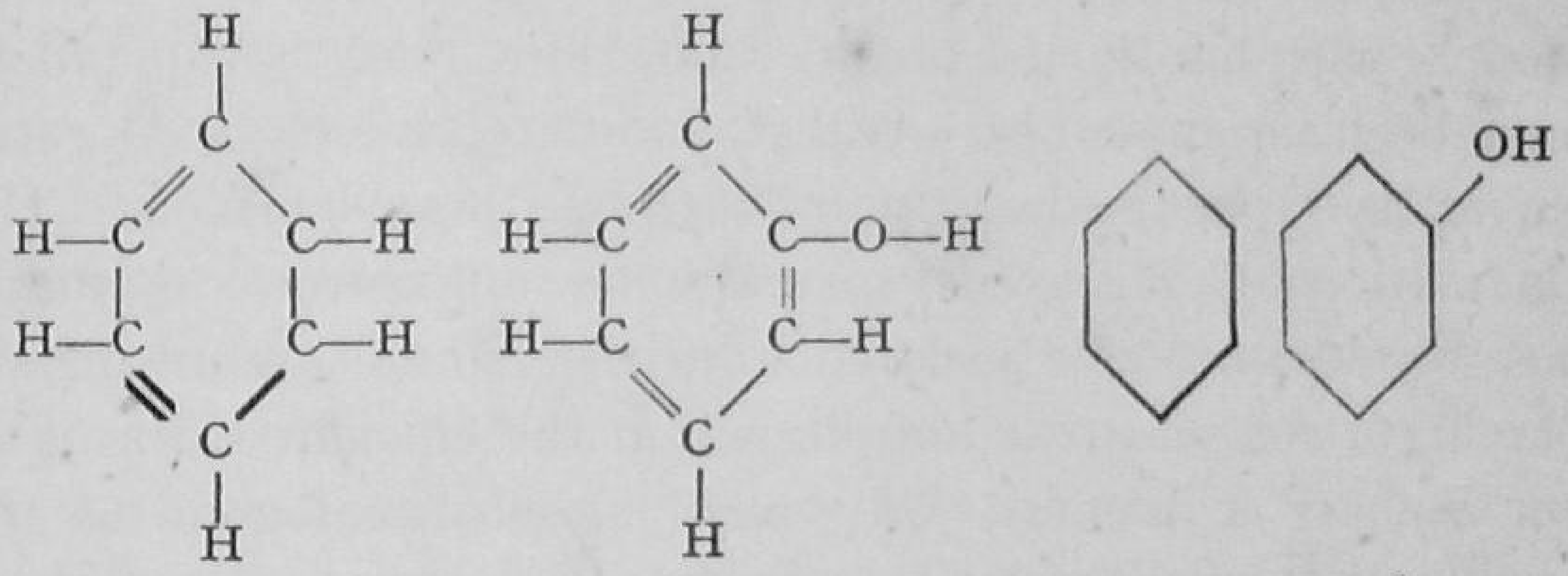
FIG. 14.—Acetylene.

contains them. We can often predict what the properties of a compound not yet made will be, because, from its formula, we can recognize the groups which it will contain. Any compound, for example, which carries the carboxyl group, —COOH, will have acidic properties like acetic acid, whilst any compound carrying the amino group NH_2 will be a "base" like ammonia; that is, it will tend to form salts with acids.

Sometimes in organic compounds atoms may be connected by more than one bond. In ethylene, for example, the two carbon atoms are joined by two bonds, that is to say, they share four electrons (Fig. 13). In acetylene the two carbon atoms are united by as many as three bonds, and so this compound is represented as in Fig. 14. The carboxyl group, characteristic of organic acids, also contains a double bond. A double bond resembles a group in that when it occurs in a molecule it usually is associated with the appearance of certain characteristic properties.

We very frequently meet with compounds containing three double bonds in a ring formed of six carbon atoms (Fig. 15 *a*).

The remarkably stable molecule of benzene is nothing but a ring of six such carbon atoms, each of them carrying one hydrogen atom so as to satisfy all the valencies. The group C_6H_5 containing this important ring system is called the phenyl group, and it is found, for example, in carbolic acid or phenol, which has the formula C_6H_5OH (Fig. 15 *b*). Usually, in order to simplify printing, the C and H symbols are omitted from formulae of this type, and they are written as in Fig. 15, *c* and *d*.



a *b* *c* *d*

FIG. 15.

On the basis of these ideas and a few simple extensions of them, the whole vast science of organic chemistry has been erected. The number of compounds to which definite structures have been assigned is enormous. Owing to the very definite nature of these structures and the fact that they are all capable of a relatively simple pictorial, one might say geometrical, representation it has been found possible to arrange and tabulate them in lexicons or hand-books, and the system of arrangement is so good that in most cases a few minutes suffice to enable the organic chemist to ascertain exactly what papers, if any, have been published about any particular compound in which he may be interested. When it is realized that up to the present the list contains perhaps half a million compounds, it will be understood how great a triumph of orderly arrangement and of indexing this is, and how striking a vindication of the correctness of the theory

which accommodates so easily, each in its proper place, this enormous number of different compounds. Furthermore, the great majority of them have actually been synthesized in the laboratory by the chemist, and these structural formulae not only explain the properties of the compounds, but also suggest the methods of synthesis to be employed, and it is in terms of them that the reactions involved are described.

Two instincts seem to be deeply rooted in human nature—the instinct to construct things, and the instinct to solve mysteries. Most children like to build with bricks or construct models with cardboard or Meccano. Few readers can fail to have been fascinated by a really good detective story. Organic chemistry appeals directly to both of these instincts. The elucidation of the structure of some unknown compound, possibly a compound isolated from the animal organism and playing a role of great importance in the efficient working of our bodies, is in many ways very closely analogous to the working out of the solution of a detective story. One by one the various clues are collected; some of these may be important, others may be misleading, not to be accepted altogether at their face value. Sometimes an impasse seems to be reached—usually this indicates that there is a serious flaw somewhere in our train of deductions, and it suggests the need for a fresh start with an unprejudiced mind. But sooner or later the various pieces of the puzzle are found to fit together and a formula is deduced which is consistent with all the known facts.

And then comes the constructive side of the work, the attempt to build up in the laboratory a compound having the formula suggested by our previous work. The organic chemist cannot, of course, take separate atoms or even groups of atoms and piece them together like the separate parts of a sewing-machine. He is, in fact, always dealing with not one molecule but millions of millions of millions of them. However, with knowledge and experience and with a large amount of trial and error, he is able to discover under what conditions he can cause relatively simple molecules to react together to form

more complicated ones, and then how to modify these, often by very roundabout routes, until at last he reaches a compound with the structure he desires. At every stage he employs his structural formulae to help him to follow and interpret what actually happens, and very frequently he comes across minor mysteries the solution of which proves to be both useful and amusing.

But the attractions of organic chemistry are not limited by its appeal to the instincts of construction and investigation. In his everyday laboratory work the organic chemist is constantly carrying out interesting practical operations, with a technique sufficiently skilled to give pleasure in the doing of it, but not so very skilful that it can be acquired only by the very few. He sees with great satisfaction the beautiful crystals which his efforts have succeeded in extracting from some ugly, dark, sticky tar. He watches the reaction mixture melt and become liquid and change colour in all kinds of unexpected ways. He is constantly doing things—distilling, dissolving, or freezing his solid or liquid products—and all the time, corresponding to the reactions which he sees going on before his eyes in beakers and test-tubes, he has pictures in his mind of the actual atomic configurations which are involved, and of the changes which they are undergoing.

Those are the academic attractions of the science. Let us look at the other side of the picture. It is obvious that organic chemistry occupies a key position in modern life. This structural theory which we have been discussing has made possible the development of great chemical industries during the last seventy years or so. The production of synthetic dyestuffs, of explosives and of synthetic drugs has had a profound effect on present-day civilization. Aspirin and indigo, mustard gas and T.N.T. (trinitrotoluene) are all products of the organic chemist.

The ultimate object of the science of biochemistry is to interpret the various activities of the living organism in terms of precise chemical reactions taking place between substances

of definitely known chemical structure. Progress here is obviously impossible until the compounds present in the living tissue have been discovered and their constitution ascertained. It is for this reason that the most important recent advances in biochemistry have been in the direction of isolating and establishing the constitution of compounds playing an important role in the metabolism of the living organism. Perhaps the most outstanding examples are to be found in connexion with vitamins and hormones. During the last twenty years the progress achieved has indeed been immense. Often within the space of a little more than a year a compound has been isolated, its structure completely elucidated, and then a product of this structure synthesized and proved identical in its chemical and biological properties with the natural compound. Here, the type of problem involved and the technique used are essentially those of organic chemistry, although the object of the work is biological.

It is of interest to inquire what has made possible this very rapid progress of the last two or three decades. It depends largely on a purely technical development—the advent of micro-analysis. Up to about thirty years ago the analysis of an organic compound—the determination, for example, of the percentages of carbon and hydrogen which it contained—required at least one-tenth of a gramme, that is to say, one hundred milligrams. As the result of the work of Pregl, an Austrian chemist, it is now possible to carry out an analysis with three to five milligrams, about one-twentieth or one-thirtieth of that previously required, and the results are practically of equal accuracy. This development has effected an immense saving of time and labour, especially in the case of compounds of high biological activity. These usually exist in the animal or plant in extremely minute amounts, and so they can be obtained even in quantities of a few milligrams only with extreme difficulty. Thus it makes all the difference if work can be done with a few milligrams as contrasted with the few hundred milligrams previously required.

All structural formulae rest ultimately on the analysis of the compound in question. Thus the development of micro-analysis has made possible the investigation of many substances which previously it would have been almost hopeless to tackle. Further, now that micro-analysis has enabled chemists to analyse these very small amounts, apparatus and methods of manipulation suitable for these quantities of material are available and a whole science of micro-organic chemistry has developed.

And how far, we are moved to ask ourselves, will the chemist be able to go in this direction? The physicist can detect a million (10^6) atoms by means of the spectroscope, and can even make quantitative estimations with amounts of this order; in radio-active processes a single atom can often be detected; the routine micro-analysis is still very far from obtaining results with amounts of substances of even the former order, for one milligram of a substance contains about a million million million (10^{18}) molecules. True, some compounds give colour reactions so sensitive that they can be detected and even measured when present in quantities of the order of a few microgrammes (1 microgramme$=1/1{,}000$ of one milligramme, or 10^{-6} gramme), but even this minute amount contains as many as about 10^{15} molecules. We should have to step about 15 places further down our scale of sizes in order to deal with single molecules. In the course of time great advances may be made in the technique of analysis, and micro-analysis may be succeeded by ultra micro-analysis and this by a super-ultra variety, and so on, but it is very doubtful if it will ever be possible to analyse a single molecule or even a small group of, say, four to five molecules.

Indeed, it may be said that the complete specification of a single molecule is essentially impossible. For, as we have seen, every time we observe an electron, we definitely affect its state; we cause it to change, either its position or its velocity or both. In as far as a molecule is built up of protons and electrons, the same principle will apply, and the more precisely

we try to locate its various parts, the more shall we disturb it from its initial state. We can analyse a crystal of sodium chloride by means of X-rays, but this is because even a small fragment of this crystal contains billions of similar atoms arranged according to a definite pattern. It is the repetition of this pattern over and over again which makes its investigation a relatively easy one. If in the piece of material under investigation the pattern is repeated only a few times, the results obtainable become less precise; the X-ray photographs obtained are literally blurred. The methods of chemistry are less direct than the process of observation by means of X-rays, but they are subject to the same kind of limitation, and so there would seem to be a limit to the detail which we can ever hope to attain with regard to the fine structure of highly complex matter.

In a strict sense, every living organism, every tissue and cell in its body is a unique structure, for no two living organisms are exactly alike. Complete knowledge of a single organism is therefore unattainable, even theoretically, for the necessary observations would inevitably destroy the organism itself. As in the case of the single electron, this essential lack of precise knowledge is intimately related to the apparent unpredictability of behaviour of living things.

But a living creature, though a unique object, is constructed of units which are replicated in large numbers. Nature fortunately is economical in her methods. Even complex structures are turned out by the mass, a highly complicated molecule of serum protein or of egg-white has millions upon millions of twin brothers almost if not quite identical with himself. It is in virtue of this almost unlimited multiplication of identical structures that progress in the detailed analysis of living systems is possible, for science is essentially statistical and cannot deal with the unique.

In the light of these considerations we cannot expect our knowledge of the structure of cells and tissues and of how they work to be at all complete; it can never be so. But real

advances have in recent years been made, and made very rapidly. A general knowledge has been obtained, often supplemented by considerable detail, of the main types of structure which are found in animals and plants. Let us see on what plan these substances are constructed and discover how nature has contrived to produce such a variety of structures with so limited a range of building materials.

CHAPTER V

MOLECULAR ARCHITECTURE

IN everyday life we use the word "purity", as applied to material substances, in two distinct senses. In connexion with food or drink it implies an absence of dirt or possibly of adulterants or preservatives. On the other hand, when we speak of pure gold we mean that the metal in question consists of 100 per cent gold and nothing else. A pure substance in this sense is one which is homogeneous, and so cannot be split up by any ordinary physical method into two or more different constituents. When the chemist speaks of a pure substance he uses the word in this latter sense. It is very important to have a clear idea of the distinction; for example, milk, however fresh from the cow and however clean, would not be a pure substance as far as the chemist was concerned. On the other hand, the cane sugar which we buy from the grocer is, or ought to be, a compound of very high purity, even in the eyes of a chemist. Unlike pure gold, it does not contain atoms of only one type—on the contrary, it contains atoms of carbon, oxygen, and hydrogen in its molecule—but all the molecules contained in a lump of cane sugar are essentially identical and are all represented by the same structural formula. This is what we mean when we say that cane sugar is a pure substance.

But how are we to tell whether any particular substance is pure or not in this sense? The term "pure substance" suggests to the chemist's mind something which exists in the form of well-defined crystals all of which look alike when examined under the lens. This is not, indeed, an absolute guarantee of purity, but it is an important test.

When a compound is liquid, the establishment of purity is usually more difficult, but in general crystalline derivatives

can be prepared and in this somewhat indirect way the purity of the compound established.

When the organic chemist is asked to find out the structure of any substance, his general method is to prepare pure compounds from the material in question and then to analyse them so as to find out how many atoms of the different elements each of these pure compounds contains in its molecule. He then sets himself to devise formulae which will accommodate the results. Sometimes there may be more than one possible formula consistent with all the facts, but in that case further experiments with the production of other pure compounds usually lead to the elimination of one possibility after another until only one is left. If no mistake has occurred, this will be the correct one and will never be displaced.

But many of the substances we are most familiar with in everyday life are not pure substances in the chemist's sense—starch, meat, rubber are not crystalline, nor can they be obtained in a crystalline form. Analysis shows that they are for the most part constituted out of carbon, hydrogen, and oxygen, and in some cases, of nitrogen. How are these atoms arranged in such non-crystalline substances? In what way do these materials differ from the much more tractable crystalline compounds with which the organic chemist is so familiar?

These questions have not yet been completely answered, but much progress has been made during the last thirty years. Many different kinds of method—organic chemistry, physical chemistry, X-ray investigation—have been applied and have all shed important light on the central problem, the arrangement of the atoms in these non-crystalline substances.

When a problem of this type has to be tackled, a line of approach often very fruitful is to try to break down the complicated structure into smaller, simpler fragments and then to investigate the nature of these.

It is important to break up the large molecule by methods as mild as possible, in order that there should be a reasonable probability that the fragments retain the same essential

structure which they possessed when they were parts of the larger molecule.

When this process is applied to a "protein" such as forms the characteristic constituent of meat, blood, or the white of eggs, it is found that the main products are organic compounds belonging to a special class called amino-acids. This name indicates that they are acid in nature, in other words that they contain a carboxyl group (—COOH), and in addition an amino group (—NH_2); they can thus function both as acids and as bases (see p. 60). One of the commoner amino-acids is called alanine and possesses the formula

$$\begin{array}{ccc} NH_2. & CH & .COOH. \\ & | & \\ & CH_3 & \end{array}$$

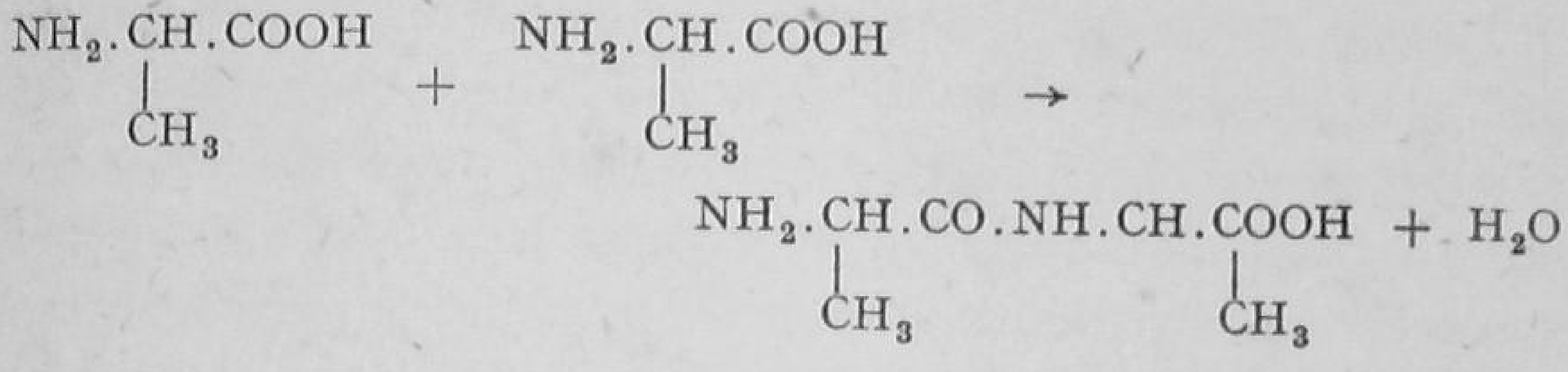
Many other amino-acids are known; about two dozen altogether have been separated from the scission products of proteins, and the establishment of their exact structure has in some cases involved very considerable labour. However, they are all crystalline compounds or yield crystalline derivatives, and the discovery of their structure, while requiring patience and skill, has been effected by the classical methods of organic chemistry without any insuperable difficulty being encountered. They all prove to be of the general type

$$\begin{array}{ccc} NH_2. & CH & .COOH, \\ & | & \\ & X & \end{array}$$

where X is some fairly simple group, or "side-chain". Thus, when X is the methyl group (CH_3) we obtain the formula of alanine given above; when X is a hydrogen atom the formula represents the simplest of all the amino-acids, glycine, $NH_2.CH_2.COOH$. All the other amino-acids are evidently derivatives of glycine. The next step is to find out how these various amino-acids are united together in the protein molecule.

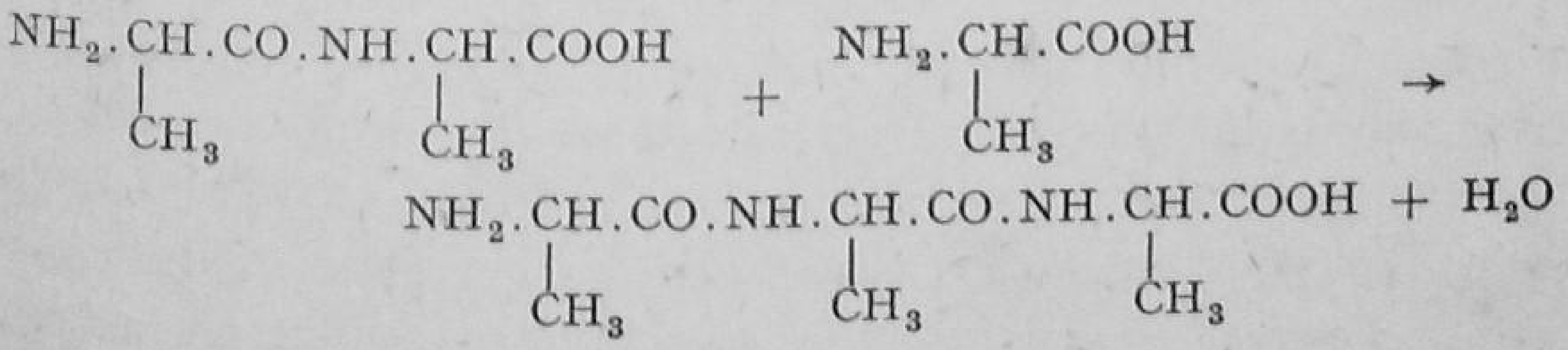
It is now about forty years since the great German organic chemist Emil Fischer concentrated his energy and skill on this difficult task. He was able to show that, in all probability, the amino-acids are joined together by what is called an

"amide linkage". Let us, for example, consider the very simple amino-acid alanine. We may imagine two molecules of this amino-acid to react together with the elimination of water so as to yield a compound of almost double the size, as follows:



It will be seen that the carboxyl group of the one molecule reacts with the amino group of the second, with the elimination of water, so as to give rise to the amide group —CO.NH— which retains neither the acid nor the basic properties of the original component carboxyl or amino groups. The whole compound—we call it a dipeptide—retains one free amino and one free carboxyl group, and so is still, in a sense, an amino-acid. In fact, it retains many of the properties of the original alanine; for as we explained in the last chapter, the properties of a compound depend very largely on the groups which it carries.

It is clear that this process can be repeated—that the compound made from the two alanine molecules may be further condensed with a third molecule to yield a still longer chain of atoms (a tripeptide), as follows:



This process of condensation may be repeated again and again until compounds are obtained formed out of quite a large number of amino-acids and containing a carboxyl group at the one end and an amino group at the other. Of course, the individual amino-acids in a chain need not be all of the same

kind. The first might be alanine, the second glycine, and the third any one of the other score or so of naturally occurring amino-acids. All kinds of variations are possible, and here we have one of the reasons for the extraordinary variety which we meet with in the proteins.

Though in theory it is possible to build up "polypeptide" chains of almost unlimited length, it is found in practice that the technical difficulties become more and more serious as the size of the molecule grows larger and larger. Emil Fischer succeeded in synthesizing chains containing up to eighteen acids. Dipeptides, tripeptides, and various polypeptides are met with among the products of the partial splitting of proteins, but the proteins themselves contain perhaps 250 or 500 amino-acids in their molecules and there does not seem to be any likelihood of organic chemists being able to synthesize them—at least not for a long time to come.

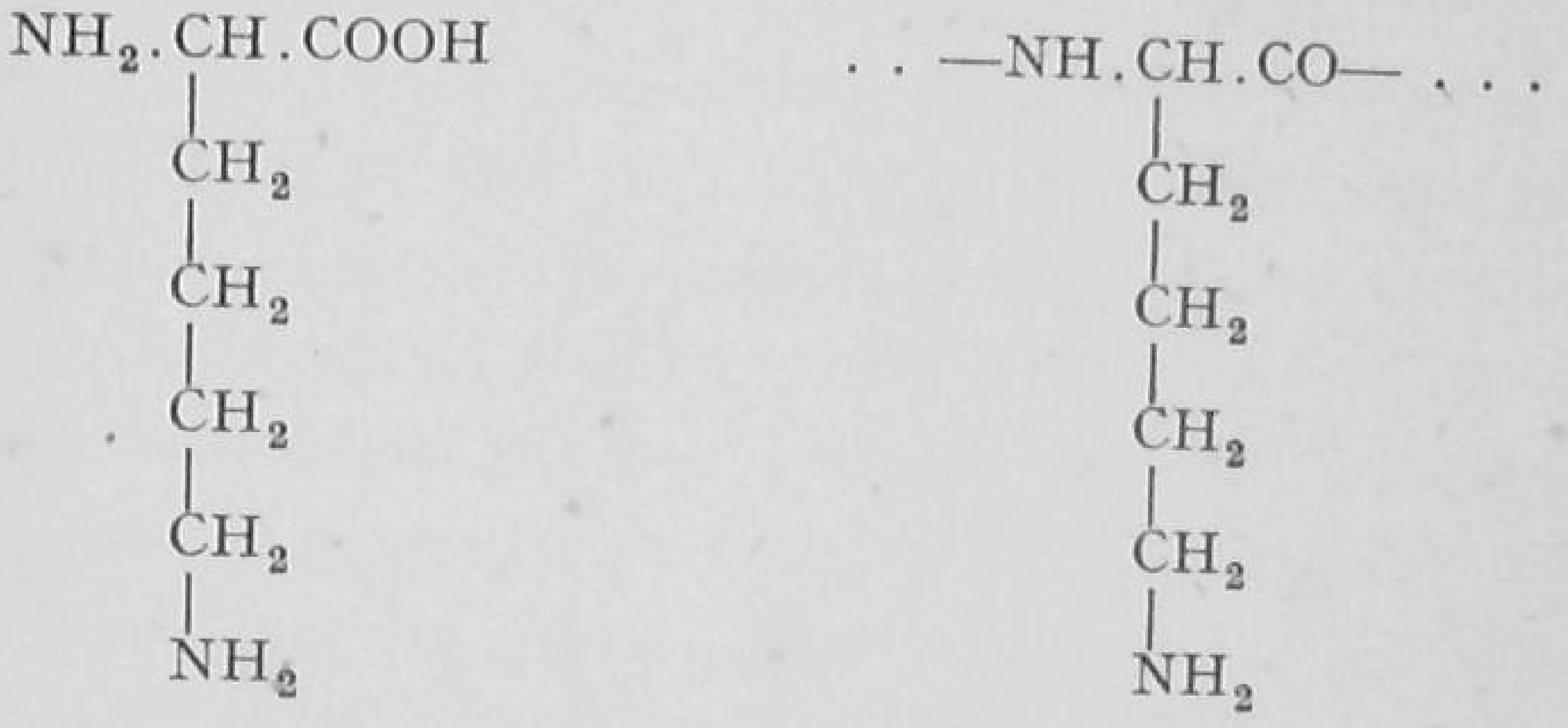
The fact that amide linkages exist in protein molecules has in more recent years been confirmed by X-ray analysis. X-rays have proved to be a very valuable weapon in the analysis of simple crystals, for it has enabled information to be obtained about the position of the individual atoms. With experience in the use of the method it has been possible to extend it to more complicated materials, and during recent years Astbury and his colleagues have applied it to the proteins themselves. The results as far as they go confirm and complement the chemical evidence. It has been definitely shown that the molecules of certain proteins consist of polypeptide chains of which the following represents a section:

$$\ldots\mathrm{NH.\underset{X}{\underset{|}{CH}}.CO.NH.\underset{Y}{\underset{|}{CH}}.CO.NH.\underset{Z}{\underset{|}{CH}}.CO.NH}\ldots$$

Regularly along the chain appear various groups denoted above by X, Y, and Z. The nature of these groups depends on the particular amino-acids which have gone to form the peptide chain; they are simply the groups which must be inserted into the simple amino-acid glycine in order to give

the amino-acids actually found in the protein molecule. A chain of glycine units would, of course, carry no side-chains at all.

The fact that proteins are derived from amino-acids by the simple process of condensation through amide linkages has some rather interesting consequences. In the first place it is easily seen that by the use of quite a small number of amino-acids it is possible to form an extraordinary variety of different peptide chains. Thus, if we suppose that there are available



(*a*) (*b*)

FIG. 16.

twenty different amino-acids, there will be almost 400 compounds each containing two of them, almost 8,000 containing three; whilst the number of polypeptides containing ten amino-acids would amount to about ten million million. In the case of a chain containing twenty units we reach the enormous number of about one hundred million million million million. These figures take into consideration only the simple peptide chains. In point of fact, the side-chains, which we represented by the letters X, Y, Z, in the last formula, may themselves carry groups which can enter into chemical combination, and so make possible further variations. As an example we may take the case of the amino-acid lysine, which has the formula in Fig. 16 *a*. When this occurs in the middle of a polypeptide chain we obtain a configuration as in Fig. 16 *b*. Evidently the side-chain carries a spare amino group, and it is clear that this in turn might be linked up with the carboxyl

group of some other amino-acid, perhaps one forming the terminal part of a polypeptide chain. The whole molecule would then appear branched, and would no longer be a simple, straight polypeptide. Many modifications similar to this are possible, so that altogether a truly amazing number of molecules may be formed out of a relatively small selection of amino-acids.

Proteins play a very important role in the economy of living organisms, and it is found that most of the more remarkable characteristic activities of the living cell are associated with the presence of proteins—often of a very highly specialized type. It is therefore not at all surprising that these substances are constructed on a plan which allows of extreme variety with relatively limited resources. And here another consideration arises. The animal derives its protein from its food. Even if the right protein were found, the task of assimilating it and transporting it in the animal's body to the place where it is wanted would present considerable difficulty. As things are, an animal need only eat one or two suitable proteins, break them up by digestion into their component amino-acids, and then proceed to build up its own proteins where they are wanted out of the assorted amino-acids which the blood has brought from the digestive tract.

The existence of animals of the kind we find on earth is rendered possible only by this easy method of acquiring proteins, a method which depends on the amino-acid chain architecture. It must not, of course, be imagined that these proteins have been synthesized by the plant for the special purpose of providing food for animals. The plants have built up their proteins on the polypeptide pattern presumably because they found it practical and convenient to do so. The animals which came along found that the plant proteins could easily be split up into simple units consisting of amino-acids, which rendered them readily assimilable and capable of being used for the building up of just those structures which they themselves required. For the animals also the easiest plan

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was to construct proteins out of amino-acids by means of peptide linkages. Now it is just conceivable that some animal species might have evolved which built up its proteins on some novel pattern. Such proteins would be unsuitable as food for animals of the conventional type, and so beasts of prey would have no interest in catching and killing such a species. The abnormality would possess a very high protective value. A device of this kind has actually been adopted by certain bacteria. The anthrax bacillus, for example, protects

$$\begin{array}{l} COOH \\ | \\ CHNH_2 \\ | \\ CH_2 \\ | \\ CH_2 \\ | \\ COOH \end{array}$$

FIG. 17.—Glutamic Acid.

itself with a capsule consisting of a protein of extreme simplicity made up of the amino-acid glutamic acid (Fig. 17). Certain unusual features in the architecture of this capsular protein render it very resistant to the agents with which the body usually disrupts foreign proteins, and so the capsule forms an efficient defence for the bacterium. But the higher organisms do not seem to have found it practicable to make use of a similar device, and the result is that plants and animals alike have built up their proteins on the same general pattern and out of the same assortment of amino-acids.

All proteins, then, are constructed on the same general pattern—all are built up out of amino-acids joined together by peptide linkages. But this is not the whole story. Some proteins, for example, contain a sugar molecule in combination with the condensed amino-acids. Others, such as haemoglobin, are formed out of two parts, the one being a typical protein formed by the condensation of amino-acids, the other a completely different structure. These modifications super-imposed

on the basic polypeptide pattern help to increase the variety of form and behaviour which the different proteins may exhibit. They are particularly useful when a protein is required to perform some specialized function—such as the carrying of oxygen in the blood in the case of haemoglobin. But such modifications must be regarded as secondary—the polypeptide pattern of amino-acids is fundamental.

Once a general idea of the structure of the protein molecule has been obtained by the chemist, the next step is to discover its size. But first of all we have to be clear about what it is that we want to measure. In the case of ordinary compounds with relatively small molecules, it is usually assumed that when the substance is dissolved or is in the vapour state, it exists as single molecules, so that the particle weight in the gaseous or the dissolved state may be taken as the molecular weight. Occasionally this does not hold even with simple compounds, but by using a variety of solvents such exceptions can usually be detected, for, if there is "association" of the molecules, this is not likely to be the same in all solvents. Now many proteins, especially the more important ones, are not soluble in solvents other than water, or if they are they deteriorate rapidly in solution and cannot be recovered in the original state. Thus even if we find the weight of the particles which exist in aqueous solution, we cannot be sure that this is really the molecular weight. However, it is a very important step in the right direction, for the molecular weight, if not actually equal to the particle weight, is likely to be some simple aliquot fraction of the latter, such as one-half or one-third.

There are several methods which may be employed for the determination of the particle weight of proteins in solution, but the method developed during the last twenty years or so by the Swedish Nobel Prize winner Svedberg is simple in principle and of very general applicability.

It is common experience that if a shovelful of earth is stirred up in a pailful of water, the stones in it sink instantly

to the bottom. Particles of sand may take a few seconds to fall out of suspension; finer particles, chiefly of clay, will take a day or so to sediment. Other things being equal, the time taken to sediment will be the greater the smaller the particles. But it is also common experience that, however long we wait, some constituents of the earth never sediment out. The water remains brown and slightly turbid. The reason for this might, of course, be that this suspended material had the same density as water and so tended neither to rise to the surface nor fall to the bottom. It is quite possible to make suspensions the permanence of which depends on this fact, but they are rare. The explanation of such permanence is usually a different one: particles of a size so small as to be comparable with a water molecule are buffeted about in the water by collisions with water molecules, and such particles cannot sit quietly at the bottom even if they get there. At the best they may tend to collect at the bottom end of the pail, but their own jerky "Brownian" movements (visible evidence of the perpetual thermal agitation of matter) will not allow them to settle down permanently.

Whether any particular suspension will sediment or remain in this equilibrium state depends on several factors, such as the size of the particles, the gravitational force, and the relative densities of particle and fluid. A suspension stable on this earth might sediment if it were transferred to the surface of the planet Jupiter, where the gravitational force is almost three times as great. Now if we are presented with a stable suspension of very minute particles such as a protein solution we cannot of course take it to Jupiter in order to make it sediment, and so by measuring its rate of settling out obtain information as to the average size of the individual particles; but we can produce an equivalent result in a somewhat different way, namely, by making use of the so-called centrifugal force.

If we swing round a corner rapidly in a car, we tend to be flung outwards; a flywheel running too fast may burst as the

result of the enormous force with which the quickly revolving parts tend to fly off. If we attach the vessel containing our suspension to a flywheel, it will experience the same effect as if it were in an intense gravitational field. With a fixed radius the strength of the field will increase with the square of the speed of the rotation, so that, with high speeds, enormously strong fields can be produced. The ordinary centrifuges of the laboratory rotate at a few thousand revolutions per minute. This results in the production of fields of about a hundred times the force of gravity. They are able to bring about the sedimentation of relatively coarse material, such as cells or bacteria, though, of course, the time required depends on the size and density of the particle.

But the particles present in most protein solutions are much smaller and show no tendency to sediment in an ordinary centrifuge. Svedberg therefore designed, and had constructed in his laboratory in Upsala, what is called an ultra-centrifuge —which is essentially a centrifuge working at a much higher speed than an ordinary one. His machine could revolve at a speed producing fields up to 200,000 times that of gravity. Naturally, the engineering difficulties in the construction of these machines are considerable and many problems of detail crop up in carrying out the actual experiments, but the principle involved is simple and relatively straightforward.

This ultra-centrifuge method of Svedberg has now been applied to many different proteins. It may be mentioned that by suitable calculations some information can be obtained about their shapes as well as their sizes: whether they are approximately spherical or more like plates or rods. It is found that in the case of some proteins the particles are not all of the same size, but vary over a considerable range. This is shown by the fact that the particles in such a solution do not all fall at the same speed; gelatine and casein belong to this group. However, many proteins are found to dissolve in water to give solutions the particles of which are of very uniform size. Of these proteins two main types may be

distinguished. There is a group of "giant" proteins which form relatively large particles, the weights of which are one to ten million times that of a hydrogen atom; that is to say, these particles appear between point 6 and point 7 on our scale of sizes (p. 9). An important member of this group is the copper-containing substance haemocyanin, which performs much the same function in crabs and snails as haemoglobin does in the higher animals. Of the proteins of the second type the particles vary in size from 10,000 to several hundred thousand times that of the hydrogen atom. Table II summarizes some of the results.

TABLE II.—SOME PROTEINS AND THEIR PARTICLE WEIGHTS

(These values are only approximate; in some cases the experimental values vary over a considerable range.)

Protein	Particle weight
Gliadin (from wheat)	27,000
Insulin	41,000
Egg albumin	40,000
Haemoglobin	67,000
Serum albumin	70,000
Serum globulin	160,000
Amandin	330,000
Edestin	300,000
Haemocyanin (crab)	2,000,000
Haemocyanin (snail)	5,000,000
Bushy stunt virus	7,600,000
Tobacco mosaic virus	60,000,000

But how should we picture a typical protein in solution? There is no general answer to this question, for proteins differ so widely amongst themselves. Some proteins, indeed, such as those which make up the hair or skin of an animal, do not dissolve at all. Of those proteins which do dissolve in water, egg albumin is a good example. It is the chief protein present in the white of an egg before it is cooked. The results obtained by means of the ultra-centrifuge show that we must think of a solution of this protein as containing an enormous number

of particles each really very small, though large as compared with the molecules of water by which they are surrounded. Each protein particle will in fact weigh about 40,000 times as much as a hydrogen atom or about 2,000 times as much as a water molecule. The ultra-centrifuge measurements also show the particles to be approximately spherical in form, so that their linear dimensions will be about twelve times those of a water molecule. These small protein particles are all very much alike. This follows, not only from the uniformity in their size, as demonstrated by the ultra-centrifuge, but also from the characteristic and unvarying behaviour of solutions of egg albumin. There is also the important fact that in certain circumstances the protein separates from solution in a crystalline condition. Now we have learned to recognize the crystalline state as specially characteristic of pure, homogeneous substances, though, in the case of large molecules such as those of proteins, we cannot without reservation apply the principles we have learned from our experience with the simpler, smaller molecules of ordinary crystalline substances.

However, the various lines of evidence all go to indicate that the particles of this protein are constructed on a uniform plan, and are all extremely similar one to another. It is usually assumed that they are identical.

With regard to the detailed structure of a protein molecule, we have seen that it consists of a large number of amino-acids joined together by peptide linkages. From our knowledge of its weight it may be calculated that even in the simplest case each particle contains about 300 amino-acid molecules.

We know that these protein particles are relatively unstable structures, and are easily altered by heat or by treatment with chemicals or vigorous shaking. They lose their power of crystallizing and become much less soluble in water. We all know, for example, how egg white changes when it is boiled or whipped. The name denaturation is given to this change, and it is an important and characteristic feature of many proteins of biological importance that they undergo this

curious alteration. We may infer that those proteins which undergo this change possess a very complicated and delicate structure. Perhaps we may best think of it as a three-dimensional arrangement of polypeptide girders, built up on some definite though complicated plan. These girders bear projecting arms—the side-chains of the polypeptides—some of which may be free, but others may be connected together so as to give greater rigidity to the structure as a whole. Perhaps, as Miss Dorothy Wrinch has suggested, the "girders" are not straight, but are twisted into more or less flat rings, so as to form a two-dimensional structure with the side-chains sticking up (or down) from this. Several ways are conceivable of effecting a "cyclization" of this type, but the "cyclol" structure shown in Fig. 18 has certain attractive features. This cyclol theory has the advantage of presenting a neat geometrical model of a protein molecule; but so far there has been an absence of positive evidence to support it, and so most protein chemists have remained unconvinced. Recently Chibnall, on the basis of very careful analytic work, has drawn certain conclusions about the architecture of the protein molecule; or, as we should perhaps rather say, the protein particle. For it is the essence of Chibnall's view that the particle present in a protein solution, the particle whose size is determined by the ultra-centrifuge, is not one molecule, one long folded peptide chain, but consists of several such chains, held together by relatively weak forces. In insulin, for example, there are eighteen such polypeptide girders in the complete structure, each containing sixteen amino-acids. Each girder has a free amino group at one end and a free carboxyl group at the other. This circumstance naturally increases the acid and base binding power of the protein considerably in excess of that expected on the ordinary simple polypeptide theory or, say, the cyclol variation of it, and this excess of acid and base-binding groups is just what Chibnall finds experimentally. The disposition in space of these polypeptide girders within the protein molecule and their precise shape

and interconnexions may in due course be revealed by X-ray analysis and the other modern physical methods for elucidating detailed molecular structure.

But whatever the details of the architecture, the structure

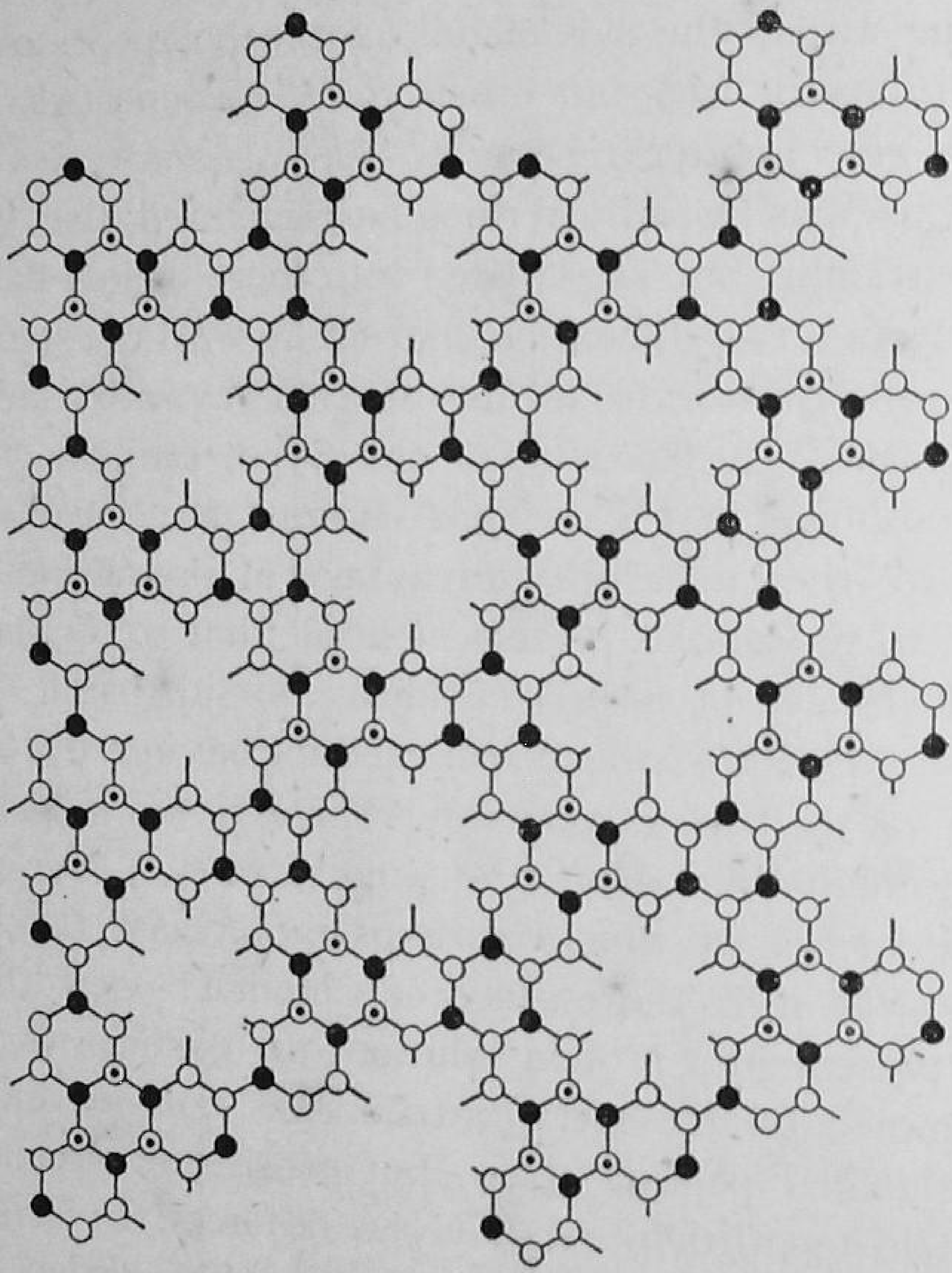


FIG. 18.—Possible pattern of protein structure according to D. Wrinch. ● signifies N atom. ○ signifies C(OH) group with OH directed upwards, ⊙ signifies C(OH) with OH directed downwards; ○— is a CH(R) with side chain R directed outwards, and ○- is a similar group with R directed upwards.

(By permission from D. Wrinch, *Proceedings of the Royal Society*.)

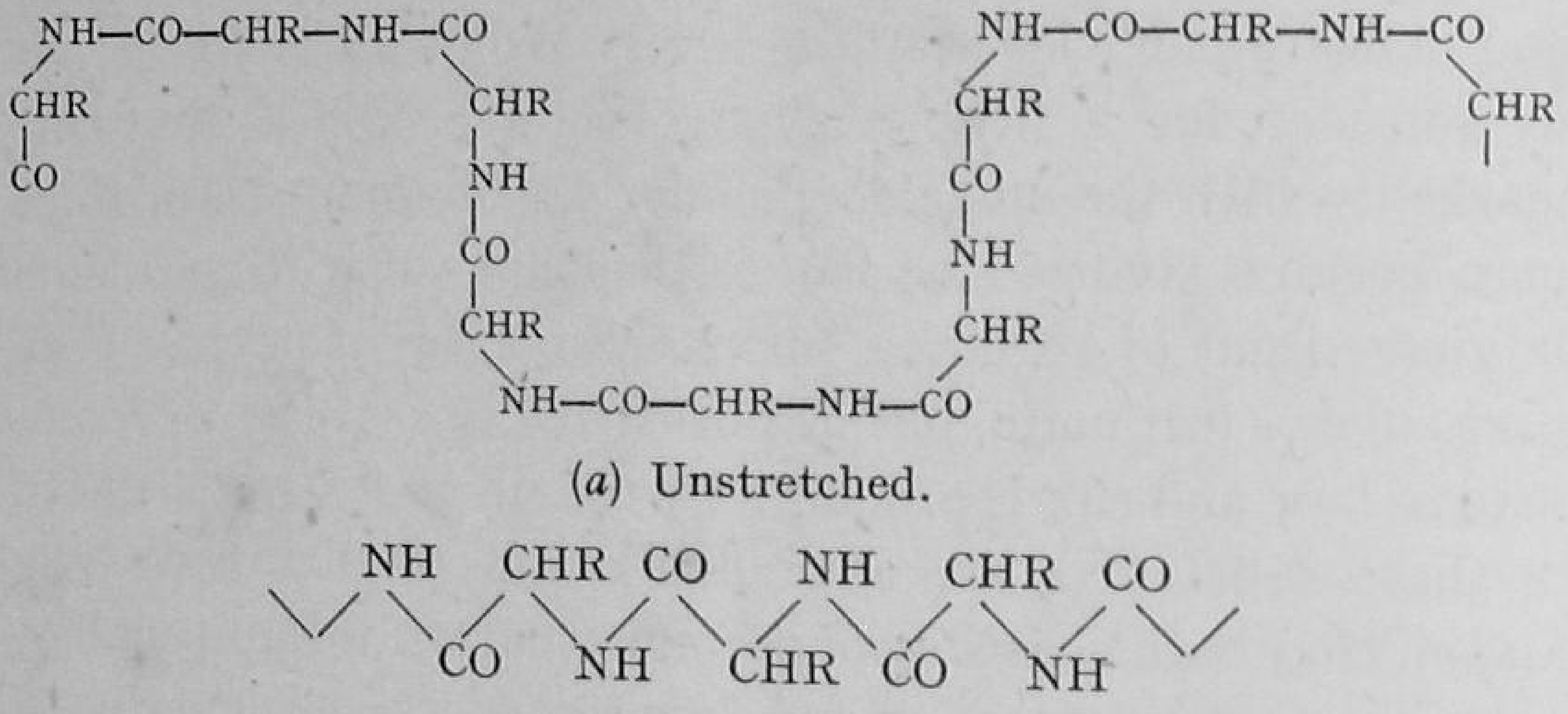
of a protein is somewhat loose and flimsy, and when subjected to increased stresses as the result of more violent thermal agitation—in consequence of a rise of temperature—some of the connecting links snap and the structure collapses. On this

view, the resulting "denatured protein" would be a mass of girders, arranged more or less parallel to one another, no longer exhibiting the peculiar properties of the original structure, though little if at all altered in chemical composition. This interpretation of the process of denaturation is suggested by the recent work of Professor W. T. Astbury of Leeds, who has examined by means of X-rays the structure of proteins before and after denaturation.

However, our knowledge of the structure of these complex and delicate particles is still in a very rudimentary state. Let us consider for a little a type of protein which contrasts markedly with the unstable globular egg albumin. Ever since man became civilized he has clothed himself with garments fabricated out of vegetable fibres or wool, or, if he has been particularly fortunate, out of silk. Wool is a variety of mammalian hair and silk is produced by the silkworm, so that both of these substances are of animal origin. It has been long known that both consisted of protein: wool of a rather peculiar, very insoluble protein called keratin containing relatively much sulphur; silk of silk fibroin. By means of X-ray examinations, Astbury has been able to indicate in what way the polypeptide chains are arranged in these fibres. Silk is the simpler case, for here, it would seem, the polypeptide chains are simply arranged lengthwise along the fibre. We are to imagine these long molecular threads as something like the separate fibres in woollen yarn; each one is very long and carries numerous side-groups sticking out from it, so that it inevitably becomes interlocked with its neighbours; the result is a very strong fibre, only slightly elastic.

The structure of a hair, however, is rather different. A hair is very elastic, especially if suitable steamed. X-ray photographs show that the stretched and unstretched fibres have quite different structures. The former is found to be rather like silk and consists of long parallel polypeptide chains (Fig. 19 *b*), but the unstretched hair contains molecules which are shorter along the axis of the hair. It seems that when the

stretched hair is allowed to shorten, the molecules develop a series of zigzag folds of the kind shown in Fig. 19 *a*. The folded, short form is called α-keratin and the long form β-keratin. A result of this folding is that the various side-chains attached to the structure (indicated by R in the illustration) appear all on the same side of the plane in which the ribbon-like zigzag molecule lies. By means of these side-chains, but especially through the sulphur atoms (we have



(*a*) Unstretched.

(*b*) Stretched.

FIG. 19.—The molecular structure of hair according to Astbury (*a*) unstretched, (*b*) stretched.

already mentioned that keratin is rich in sulphur), the molecules are tied together laterally, so as to form what is really a three-dimensional structure. These side linkages, in fact, prevent molecules lengthening and contracting freely, but treatment with steam tends to break them open; hence the increase in elasticity on steaming. However, they re-form once again when the steam is removed, and so if stretched hair is very well steamed so as to break down most of the linkages, and kept in the stretched condition, it will become fixed in that form.

These facts enable us to understand certain properties of wool and hair which are of great importance in everyday life. For example, flat pieces of woollen cloth, by the use of water and hot irons may be stretched and permanently fixed in new

apparently are long and thread-like. During the last few years, the famous Hungarian chemist, Szent-Györgyi, has separated a second protein from muscle; this he calls actin. It is not readily crystallized like myosin, and the molecules show a great tendency to aggregate together. According to Astbury, myosin has a molecular structure very like that of hair; examination by X-rays indicates that the polypeptide chain is folded in the same zigzag fashion. These muscle proteins, myosin and actin, are of very great interest, for they seem to be the most important components of the contractile muscle tissue, by means of which the multi-celled animals are enabled to move, catch food, and generally come to grips with their environment. These proteins clearly play a most important part in that mysterious process whereby chemical energy, absorbed as food and oxygen, is converted into mechanical energy. In a later chapter (p. 156) we shall describe a few clues which seem to be leading biochemists to some understanding of this crucial problem; but we must understand more of the structure of nature's engines, something of the fuel and the general set-up, before we can discuss the details of its working.

CHAPTER VI

GIANT MOLECULES

NATURE is really at heart a confirmed opportunist. There is no device which she scorns to use as long as it will give the desired results. Wasteful prodigality, savage internecine struggle, slothful parasitism, we come across them all in abundance. There is no general moral principle to be perceived in all this interesting, lurid picture of animate nature, often "red in tooth and claw", but always resourceful and infinitely varied. The only principle, indeed, to be perceived through all the confused medley is that of the extreme empiricist—that "nothing succeeds like success". The plants and animals which are best suited to their circumstances best survive. This elementary necessity is often called the "principle of Natural Selection".

The fittest animals survive and propagate their kind; they become numerous on the earth. But the whole animal includes all its parts, its anatomical structures, its special ways of functioning; all the particular mechanisms and peculiar devices which render it unusually efficient in the struggle. And the composition and structure of the living organisms we see in the world to-day is the aggregate result of all this confused interplay of forces, a curious collection of forms of the most varied type, in deciding the details of which sheer blind chance has often played a decisive role.

An animal body is, indeed, rather like the British Constitution. In many respects it may be somewhat illogical and out of date, bristling sometimes with all sorts of anachronisms, relics of an age that has passed away. But it works—that is its only excuse for surviving. However peculiar or unnatural a device may seem, it has its place and is welcome as long as it gives the right results.

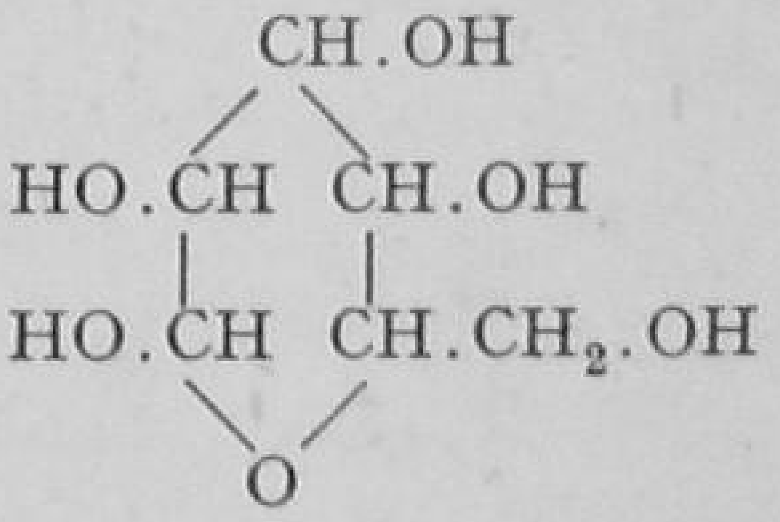
In the light of these considerations it would scarcely be expected that living bodies should always keep strictly to any general principle—either in regard to their construction or their function. They have developed as a language develops: whatever form is convenient or effective tends to be adopted. And as we know, some of us to our cost, in grammar there are usually exceptions to every rule. It is similar in the case of living matter. It is dangerous to make generalizations or lay down rigid principles. Somewhere or other in the immense variety of nature we may suddenly be confronted by some unexpected exception to perhaps the most reliable law.

But in spite of this unmanageable prodigality of life, we do find that certain general ideas or principles are met with over and over again. In the last chapter we have seen how proteins are built up of a comparatively small assortment of simple units, the amino-acids. This notion of forming large structures out of units great in number but of few types is obviously a very effective one. Man has long ago discovered how to make use of it. He constructs his houses out of bricks, his ships out of wooden planks or steel plates, his hedges out of separate shrubs. It would be surprising, therefore, if nature had not made repeated use of this same idea.

We have all learned that the three main types of foodstuffs are proteins, carbohydrates, and fats. Proteins, we have seen, are built up by a process of condensation from simple units. It is interesting to find that carbohydrates are constituted on an exactly similar plan, there being only one fundamental difference. The unit is no longer the amino-acid molecule, but an altogether different one, namely, the molecule of a simple sugar.

The sugar which most of us know best is cane sugar, obtained from the sugar cane. Exactly the same chemical substance is obtained from the sugar beet—the only difference possible between purified cane and purified beet sugar is that the small traces of admixed impurities still contaminating them may not be the same in the two cases. But cane sugar is only one

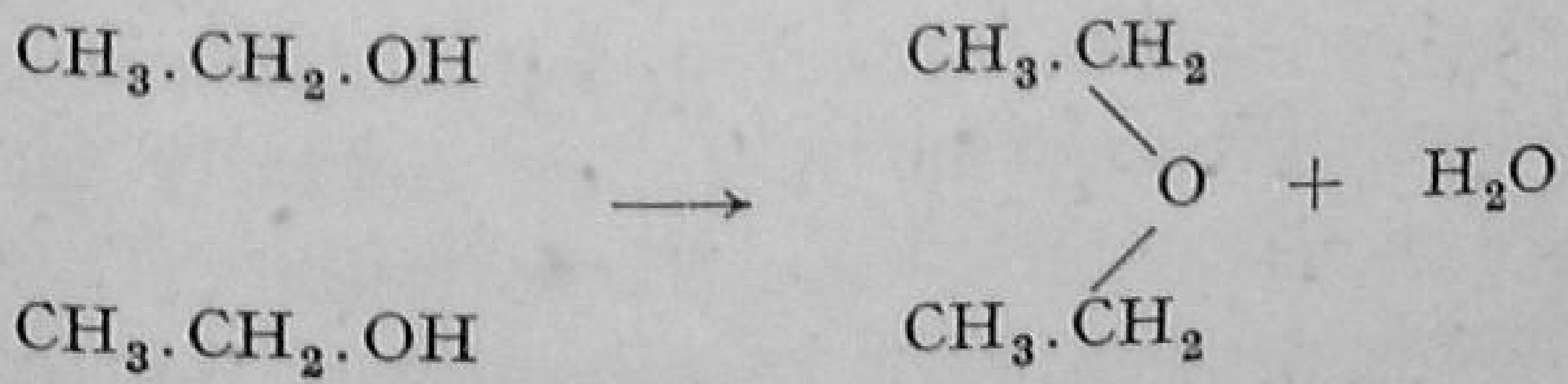
out of many different types of sugar which occur in nature. Another is that which is found in grape juice and so is called grape sugar or glucose. Actually, glucose is the sugar most frequently met with in the animal organism, and, as we shall see, it is of great importance in plants as well. It resembles cane sugar in many ways; like the latter it is very easily soluble in water, the solution having a sweet taste. It differs, however, in that it is not easily obtained in an obviously crystalline form, though under certain conditions it may be prepared as a fine crystalline powder. When glucose is analysed it is found that its molecule contains six atoms of carbon, twelve of hydrogen, and six of oxygen, and its formula is accordingly $C_6H_{12}O_6$. It can be shown that its structure is in the form of a ring and may be represented as follows:



It will be seen that the ring contains five carbon atoms and one oxygen atom. The valencies of the carbon atoms not required for the ring are utilized to join on the remaining carbon atom and also the hydrogen and oxygen atoms, the latter in the form of hydroxyl groups.

Now let us consider for a moment a simple compound which contains a single hydroxyl group, say ethyl alcohol, already mentioned as having the formula $CH_3.CH_2.OH$.

We may readily imagine that two of these molecules might combine together in this manner:



The product is a new substance containing a single atom of oxygen, the other having been eliminated as part of a molecule

of water. This reaction can actually be carried out, and indeed the product is none other than the well-known anaesthetic, ether, so often used in surgery along with the more powerful, but more toxic, substance chloroform. The process of preparing ether from alcohol may be compared with the combination of two amino-acids to form a peptide containing an amide linkage, which also takes place with the elimination of water. The idea may be at once extended to the case of two sugar molecules. Two hydroxyl groups, one from each molecule, may join together with the elimination of water, and in this way a new compound is obtained, as shown in the following equation (Fig. 20):

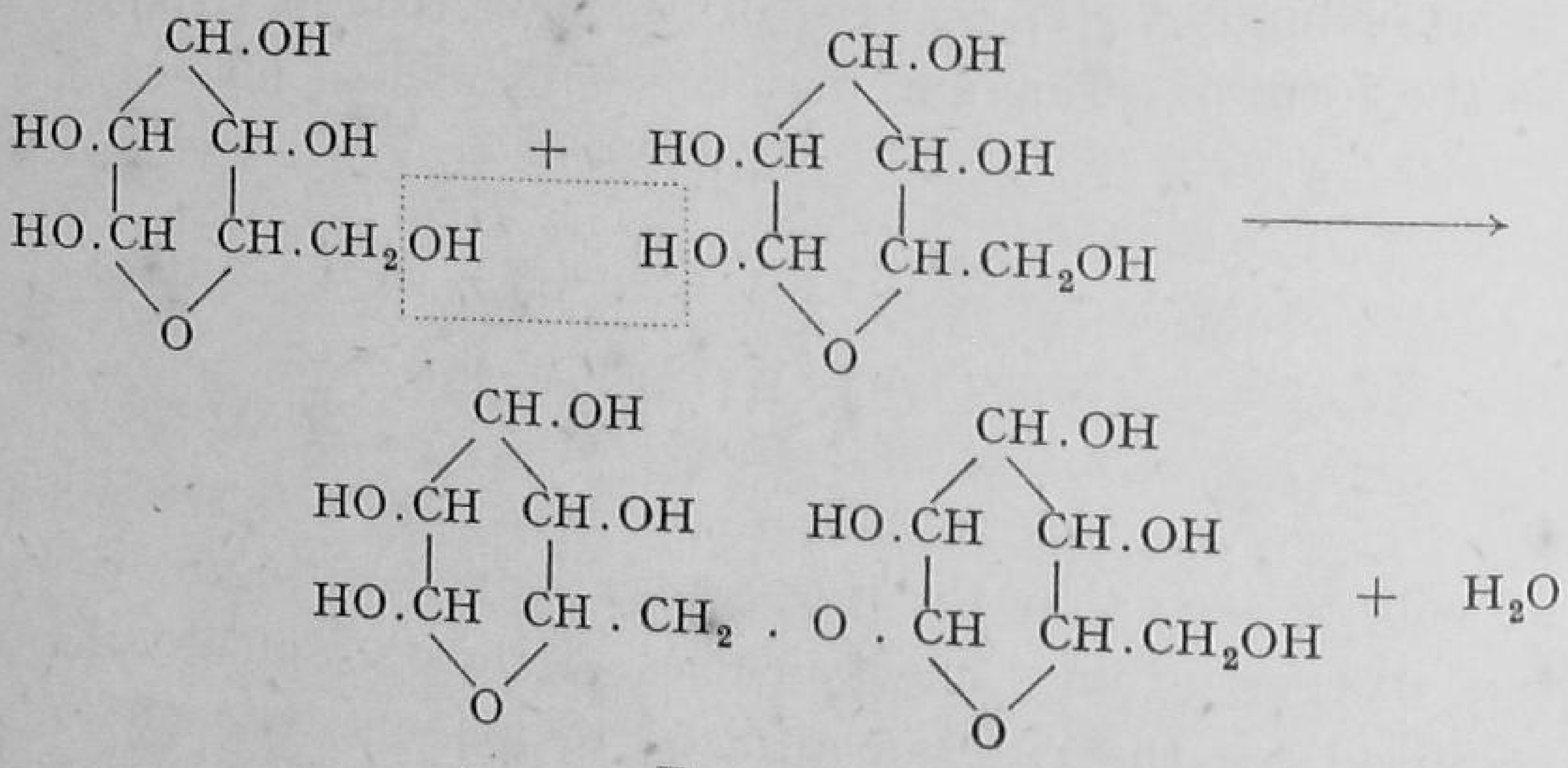


FIG. 20.

It is evident that, beginning with two molecules of glucose, we may combine them in a large number of different ways, for we may select any one of the five hydroxyl groups of molecule number one and combine it with any one of the five of molecule number two. It is not difficult to show that this would give us fifteen distinct compounds, all of which would contain twelve carbon atoms, twenty-two hydrogens, and eleven oxygens. However, there are actually many sugars other than glucose which have the formula $C_6H_{12}O_6$. All of them resemble each other in a general way, but each has its own characteristic properties. If two molecules of any of these sugars combine together—the two molecules may be of

different types—through their hydroxyl groups, in the way just described, with the loss of a molecule of water, we obtain a compound of the formula $C_{12}H_{22}O_{11}$. Evidently, therefore, an enormous number of sugars of this formula are theoretically possible. Being formed from two molecules of simple sugars (or "monosaccharides") they are called disaccharides.

A large number of such disaccharides is actually found to exist in nature. Amongst them is our old friend cane sugar. The cane sugar molecule breaks up when the substance is heated with acid into the two simple sugar molecules from which it was originally formed. One of these is glucose; the other is a somewhat different sugar called fructose. Thus cane sugar is a disaccharide formed from glucose and fructose by the elimination of water.

A great deal of patient and laborious work was required in order to ascertain how these two sugars are combined together, but now this problem has been completely solved. We need not concern ourselves here with the details.

Just as the simple sugars contain a number of hydroxyl groups in the molecule, so, too, do the disaccharides. Clearly, then, we may add on to them a third molecule of simple sugar with the elimination of water, so as to produce a trisaccharide, containing eighteen carbon atoms, thirty-two hydrogens, and sixteen oxygens.

These trisaccharides, of which quite a number are found in nature, closely resemble the disaccharides and the simple sugars in their general properties. Like them, they may be combined with another sugar molecule and in this way we obtain compounds containing twenty-four carbon atoms. Clearly this process may be repeated again and again, the molecule becoming larger and larger at each successive stage. As might be expected, the resulting compounds of high molecular weight do not crystallize as readily as the simpler sugars; they are less easily dissolved in water, and they are not sweet.

Some of the representatives of this class of polysaccharides, as these compounds of relatively high molecular weight are

called, are important and familiar substances. Starch, for example, is a carbohydrate which may be broken down completely into glucose. The different varieties of starch, potato starch, rice starch, and so on, are found to consist of two distinct components; one is called amylose, the other amylopectin. The amylose, which is usually the smaller fraction, being about 20 per cent of potato starch, possesses molecules, each of which contains several hundred glucose molecules, combined together in the form of a long chain by the loss of

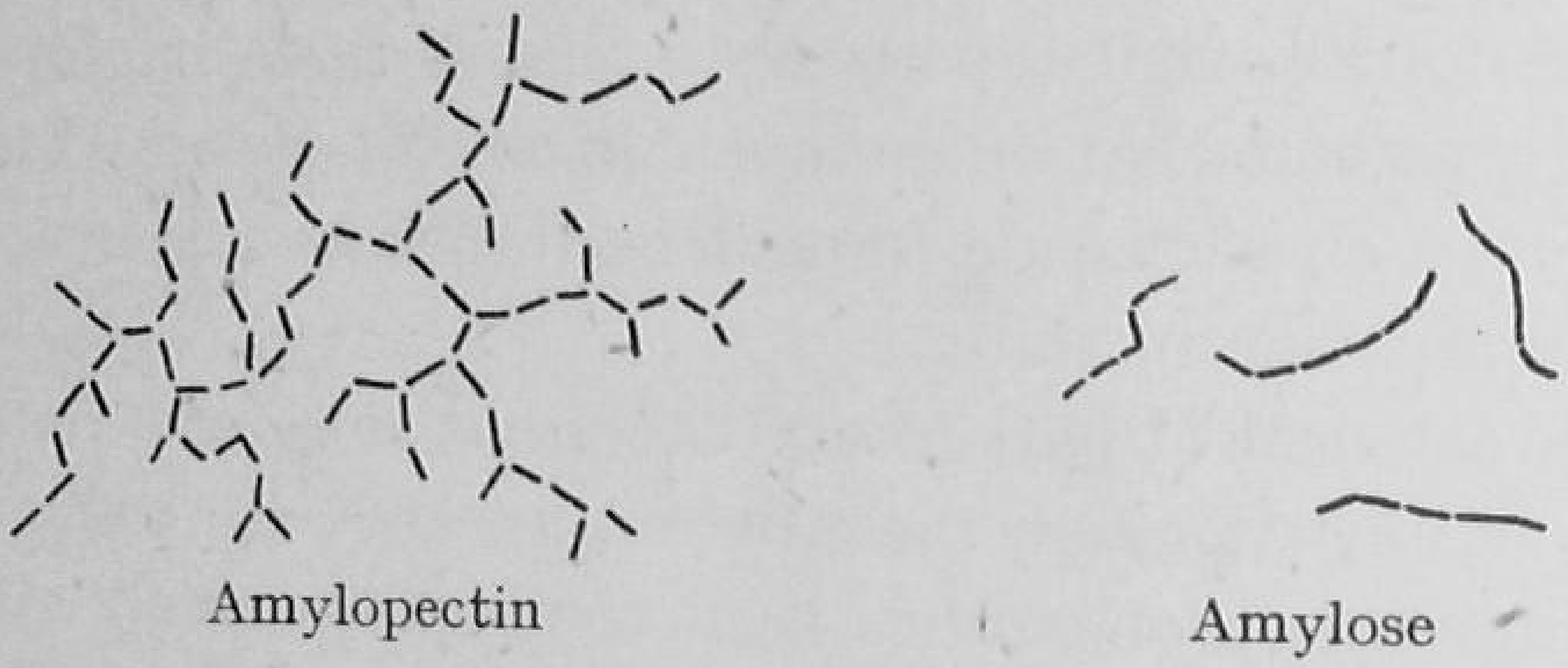


FIG. 21.—Diagrammatic representation of molecules of starch.

a number of molecules of water as already described. The molecule of amylopectin contains a considerably larger number of glucose units, but there they no longer form a straight chain; instead, there are many branch points, and in consequence a much larger proportion of glucose molecules occupying terminal places (see Fig. 21). The molecules of amylose resemble long threads, those of amylopectin are much more spherical in shape.

Starch is a characteristic product of plant life. In the animal body there is found an analogous substance called glycogen. Here again the molecule consists of glucose units linked together as in starch. The molecule of glycogen, in fact, is very like that of amylopectin, only it is even more frequently branched, and contains a larger number of glucose units. There would seem to be some tens of thousands of such units in a single glycogen molecule, so that the molecular weight reaches several millions. Glycogen gives a brown colour with

iodine; in this reaction it resembles amylopectin, which gives a red colour, rather than amylose, which gives a deep blue.

Another carbohydrate of great commercial importance is cellulose, the major constituent of wood, and familiar to us all in a somewhat impure state in the form of paper. Cotton-wool is almost pure cellulose. When broken up by suitable methods, cellulose yields nothing but glucose. The striking difference in properties between starch and cellulose—in particular the extreme insolubility and chemical inertness of the latter as compared with the former—seems to depend on the fact that the latter consists of very long chains of compactly arranged glucose units, all these chains being parallel to each other so as to form the fibre structure characteristic of the substance. These long molecules, each probably containing several thousand glucose units, are essentially unbranched, but are probably connected at intervals to adjacent molecules. It is not surprising that these bunches of long, parallel, molecular filaments which form a cellulose fibre, already closely packed and held together by considerable forces, should be highly insoluble in most solvents, and resist attack by all but the most powerful chemical reagents.

It must not be thought from these examples that all the complex carbohydrates consist of condensed glucose. The tubers of the dahlia plant contain a carbohydrate called inulin which when broken up yields nothing but fructose, the simple sugar already met with as a constituent of cane sugar (p. 91). Other complex carbohydrates found in nature contain more than one kind of simple sugar in their molecules, whilst in some the fundamental units do not contain six atoms of carbon and possess the formula $C_6H_{12}O_6$, but five carbon atoms, with the formula $C_5H_{10}O_5$. However, in spite of all this variety in detail, the general plan of the architecture of all these substances is essentially the same.

We thus see that just as amino-acids are combined together to yield polypeptides and ultimately proteins, so simple sugar molecules combine to form disaccharides, trisaccharides, and

finally complex carbohydrates such as starch and cellulose. However, whilst many proteins are unstable, highly reactive substances playing a vitally important role in the essential activities of the living cell, the complex carbohydrates are in general relatively stable, inert substances not capable of taking part directly in living processes. What, then, is their function? Most of them are storage materials. With the help of sunlight the plant synthesizes sugar from carbon dioxide and water during the summer, and must keep it in a convenient form until it may be required. It therefore condenses sugar molecules together into the relatively stable—but not too stable—insoluble product which we call starch, from which the original glucose may be easily obtained again just as it is wanted.

The case of cellulose is somewhat different. Its peculiar chemical inertness and great insolubility fit it well for the purpose it serves in the plant of acting as a structural material.

In the two examples which we have so far examined, the proteins and the carbohydrates, condensation into large aggregates proceeds with the loss of molecules of water. It is possible, however, for the same general principles to be applied in another way. Let us consider the very important case of rubber, a natural product which has acquired extreme economic and industrial importance. Natural rubber is obtained from a tree in the form of a sap or latex, which is essentially a suspension of fine droplets of the crude rubber in water. By a suitable process these minute particles are caused to aggregate and coalesce together, and the raw rubber is thus obtained in the form of a tough, elastic mass, which readily swells and dissolves in such liquids as benzene. When this raw rubber is heated with a small quantity of sulphur under suitable conditions, it gradually alters in its properties, becoming harder, less soluble, and much more durable. It was the discovery of vulcanization, as this process is called, which made it possible to use rubber in so many different ways, and especially as a material for tyres.

When rubber is heated it is decomposed into a compound called isoprene, which has the constitution

$$\begin{array}{l} CH_2{=}CH{-}\underset{\displaystyle CH_3}{\underset{|}{C}}{=}CH_2 \end{array}$$

and which is a liquid of low boiling-point with the characteristic smell associated with burning rubber. Isoprene is quite a reactive substance, and under suitable conditions, for example, when heated in the presence of sodium, it readily combines with itself to form long-chain molecules. This power of combining with itself depends on the presence in isoprene of the two double bonds; it is these which account for the reactivity of its molecules. Let us write two isoprene molecules as follows:

$$CH_2{=}CH{-}\underset{\displaystyle CH_3}{\underset{|}{C}}{=}CH_2 \qquad CH_2{=}CH{-}\underset{\displaystyle CH_3}{\underset{|}{C}}{=}CH_2$$

By the transference of a hydrogen atom from one molecule to the other and a rearrangement of the bonds, it is easily seen that we obtain a molecule containing ten carbon atoms and three double bonds. Now another isoprene may be added on to the end of this double molecule so as to produce a still larger structure containing fifteen carbon atoms and four double bonds:

$$CH_2{=}CH{-}\underset{\displaystyle CH_3}{\underset{|}{C}}{=}CH{-}CH_2{-}CH_2{-}\underset{\displaystyle CH_3}{\underset{|}{C}}{=}CH{-}CH_2{-}CH_2{-}\underset{\displaystyle CH_3}{\underset{|}{C}}{=}CH_2$$

By the repetition of this process of condensation again and again, always adding on new molecules at the end of the chain, longer and longer molecular threads are produced. This process is rather like that by which polypeptides and proteins are formed from amino-acids or polysaccharides from simple sugars. It differs from these, however, in one important respect. No molecule of water or any other substance is eliminated during the condensation process—the resulting substance gives on analysis exactly the same results as the original compound, for it contains the same relative number

of carbon and hydrogen atoms, only the molecule is many times the size of the original one.

This process of direct condensation is known as "polymerization", and it is met with, not only in the laboratory, and in industry, but also in nature. There is little doubt, for example, that the raw rubber present in the sap of the rubber tree is produced from the polymerization of simple isoprene molecules in the way we have pictured above. Natural unvulcanized rubber, in fact, is to be thought of as consisting of long molecular threads of carbon atoms, carrying hydrogen atoms and an occasional methyl group, and all twisted and matted together rather like the individual hairs in a mass of felt.

But in this instance, what can be done by the plant can also be done by the chemist in the laboratory. Substances like isoprene can be manufactured on a large scale and with relatively small cost from various natural products, including ordinary starch. When these compounds are made to polymerize under controlled conditions the result is a product very similar to natural rubber. As we all know, this production of synthetic rubber is an achievement of extreme industrial, and even political, importance. It happens that rubber trees can be cultivated satisfactorily only in certain moist tropical countries. The nations which have no control over these rubber-producing countries are therefore dependent for their supplies of natural rubber on those which do. It is small wonder, then, that industrialized countries like Germany and Russia have concentrated much effort on the development of the manufacture of synthetic rubber on a commercial scale. In consequence the production of synthetic rubber has increased during the past ten years by leaps and bounds. During the recent war the United States rapidly developed a synthetic rubber industry to replace the natural sources temporarily lost to the Japanese.

The development of synthetic rubber during and before the war was stimulated by military and political considerations.

Generally speaking, the cheapest source of rubber appears still to be the rubber plantation. But the manufacturer has at least one trump-card up his sleeve. He can produce not only ordinary rubber, but many other kinds beside. For it happens that the process of polymerization can be applied not only to isoprene, but also to many closely related compounds. One of these, for example, is called butadiene, and has the formula $CH_2{=}CH{-}CH{=}CH_2$. This polymerizes to give a product which differs little from that yielded by isoprene (the German synthetic rubber "Buna" is polymerized butadiene). Isoprene is really a methyl butadiene, that is, butadiene in which a hydrogen atom is replaced by a methyl group. If we replace the hydrogen by chlorine instead of by methyl we obtain a chloro-butadiene ("chloroprene"), and this too polymerizes to give a rubber-like product, sold commercially as "Duprene" or "Neoprene". However—and this is the important point—the product is not quite the same as natural rubber. It can be vulcanized, but it has properties not possessed by the latter. In particular, it is more resistant to many chemical reagents. Thus, Neoprene is superior to natural rubber for certain purposes and so, quite apart from the question of price, its production marks a real economic advance.

We see, then, that there are many varieties of rubber, all belonging to one large family of substances. Their similarity in properties, however, is one which depends not on chemical composition but on the possession of a common thread-like type of molecular architecture. All these rubber-like substances are formed by the polymerization of butadiene or some closely related compound; from any one of these we can obtain a whole series of polymerides, as these condensed substances are called. In those which are first formed, the molecular threads are comparatively short, whilst under other conditions the process of condensation proceeds further and the individual molecular fibres are then very long, and may contain as many as a thousand isoprene or butadiene units. The properties of

this molecular "felt" or "cotton-wool" will naturally depend very much on the length of these separate fibres. When these are not too long, the substance dissolves readily in organic solvents such as benzene to form relatively mobile solutions, but when the threads are very long the substance dissolves very slowly, and the resulting solution is viscous and sticky. It is easy to understand that the long thread-like molecules spread throughout the benzene have the same effect as a mass of slimy filamentous fungoid growth in a pool of water; in both cases the liquid is difficult to stir, and shows a great tendency to form fine threads when pulled out.

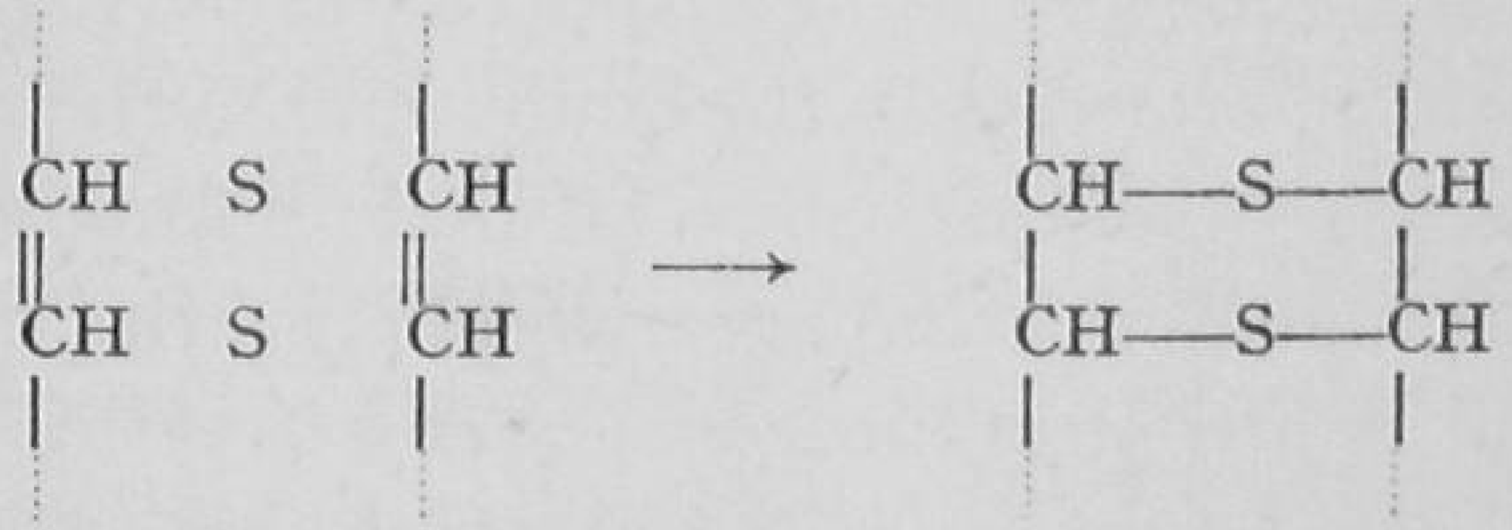
This gives us a picture of raw, unvulcanized rubber, and the closely related synthetic materials. But how are we to explain vulcanization in terms of atoms and molecular structure? For long this important manufacturing process was purely empirical and not at all understood. The process is a rather remarkable one. The rubber is heated with as little as 0·5 per cent of sulphur, and the change in physical properties which ensues is most striking. It is still elastic, but much more rigid and solid. It does not melt so readily on heating. In particular, it no longer swells so as ultimately to dissolve in solvents such as benzene. It may indeed swell a little, but it retains its original shape and refuses to go into solution. How can the trace of sulphur make all this difference?

To answer this question we recall the picture of raw rubber, a mass of long fibres all matted together, but each really free and separate from the others. It is easy to see that this felted mass can be converted into a much more rigid structure in a very simple way. All that has to be done is to knot together the fibres here and there throughout the mass. Superficially there will not seem to be very much change. The material will still be soft and elastic, but we shall find it much more difficult or even impossible to tease it apart. A relatively small number of knots will hold it together and give it a certain rigidity and compactness.

And so the function of the sulphur must be to tie together

the separate molecular fibres—not in any systematic order, but simply to make a link here and there at random between different fibres which happen to be near each other.

It is not difficult to guess how this linking of the molecular fibres by sulphur takes place. As we have seen, each fibre contains a large number of double bonds which occur at intervals throughout its whole length. Double bonds always tend to be reactive, and in particular they react readily with sulphur. The atom of sulphur can thus function as a connecting link between two threads, after reacting with them in some such way as this:

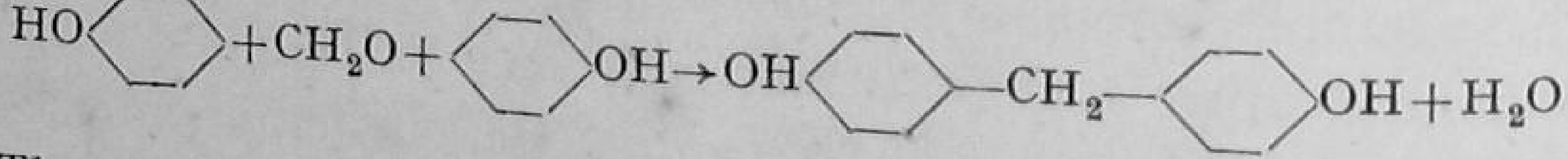


It is only within recent years that we have begun to realize the great commercial possibilities of the processes of condensation and polymerization, and of the giant molecules which are thereby produced. Nature for countless ages has made use of these simple reactions for the purpose of storing foodstuffs and fabricating structural materials such as cellulose. Man has become aware that he too can put these reactions to good use, and in consequence an enormous amount of investigation has recently been carried out on the subject. In the course of this work all sorts of curious and interesting products have been prepared—from the artificial rubber already mentioned through various elastic and plastic materials to artificial glasses, as well as electrical insulating materials of unique quality. Some of these substances have already attained great commercial and technical importance. There is, for example, the group of bakelite resins, formed by the condensation of phenol (carbolic acid) and formaldehyde, the simple compound of formula CH_2O commonly met with in the form of its aqueous solution, formalin. It is not necessary here to enter

into the details of the reaction that takes place. The underlying idea is one with which we are already so familiar—the stepwise building up of a big molecule from a large number of similar components.

The structure of these phenol-formaldehyde resins reminds us of a common children's toy called pic-a-brick. This consists of a large number of wooden blocks, each having a hole in each of its six sides. Small pins are provided which fit exactly into the holes, and any two blocks can be joined together by means of a pin. By means of another pin we may now join on a third block, and we may extend the chain of blocks as far as we please, one pin being required for each join. If we like, we may have branches in the chain, and even complicated three-dimensional structures may be built without difficulty. Obviously the more cross-linkages we put in, the more stable and rigid will be the structure.

In the bakelite resins we are to think of the wooden blocks as representing the phenol molecules, and the small pins the formaldehyde. For it happens that the formaldehyde readily pins together two phenol molecules according to the following equation:



The exact course of the reaction, whether we obtain simple chains or branched ones, or more complicated rigid three-dimensional structures, depends on the precise conditions employed. Thus even with the same starting-out materials, a considerable variety of different products may be obtained.

But, of course, it is possible in practice to condense many other compounds together into large molecules besides phenol and formaldehyde. The past decade has witnessed enormous developments in the field of synthetic plastics, both in research and in commercial application. All sorts of materials can now be produced: solid and tough for structural purposes, transparent and clear for glasses for optical instruments, fibrous

material for use in the textile industry, vitreous substances with exceptionally great insulating power, and other special electrical properties. Some of the synthetic resins form valuable glues; for example, those prepared from urea and formaldehyde. They proved of very great use during the war for such purposes as the joining together of the wooden components in the structure of the "Mosquito" aircraft; it is well known that this famous machine was built largely of wood instead of steel. Glues of similar type are also very important in the production of plywood. With two products, the public have become specially familiar; these are Perspex and Nylon. Perspex is formed by the direct polymerization, that is, the direct condensation into large molecules, of a relatively simple organic compound (methyl methacrylate). It forms a transparent glass-like solid, which can be used for many of the normal purposes of glass. It has the advantage over glass that it can be readily cut and moulded; it is soluble in chloroform, and such a solution can be used for cementing pieces of perspex together. It is softer than glass, and so more easily scratched and warped; but as it does not splinter it avoids the risk of injury where that might be serious.

Nylon is interesting in that its molecular structure bears some resemblance to that of natural protein fibres. Like a protein, it consists of long chains of carbon and nitrogen atoms, the latter appearing in the form of "amide" groups. The basic material for the production of Nylon is coal; by suitable processes two compounds are manufactured, one a straight chain of carbon atoms with a carboxyl group at each end, the other a similar chain, but with an amino group at each end. As we know, carboxyl groups can unite with amino groups to form amide linkages, and it is easy to see that if equal numbers of molecules of the acid and the amine are allowed to react together, so that the carboxyl and amino groups form such linkages, the inevitable result is the formation of long chains:

$$H_2N.CH_2.CH_2.CH_2.CH_2.CH_2.CH_2.NH.CO.CH_2.CH_2.CH_2.CH_2.CO.NH.$$
$$CH_2.CH_2.CH_2.CH_1\ CH_2.CH_2.NH.CO.CH_2 \ldots .$$

Such long molecular fibres constitute the basis of nylon. It turns out that it possesses remarkable mechanical strength, and also that it can readily be prepared in many forms and so put to diverse uses. Many of these are too well known to require enumeration. Nylon has, in fact, become a household word.

But it must be remembered that, in addition to these purely synthetic big molecules, it is possible to modify the polymerized products already existing in nature, and in this way obtain new materials, some of which are of great commercial value. Thus cellulose, which, it will be remembered, consists of enormously long chains of glucose units, may be modified in various ways by relatively simple chemical processes, and the modified chains moulded into long filaments by suitable mechanical means. In this way we obtain artificial silk, which differs from natural silk chiefly in that the polypeptide chains of the latter are replaced by the chains of condensed glucose units, slightly modified by the chemist so as to give a product with the right physical properties. Artificial silk is just silk built out of sugar instead of amino-acids.

Another example of the modification of a naturally occurring product is to be found in "chlorinated rubber". This is natural rubber treated with chlorine gas (as distinct from the Neoprene referred to on p. 97), and is manufactured in Great Britain under the name of Alloprene. Actually, it contains chlorine to the extent of nearly two-thirds of its weight. The process was developed technically during the slump years, when rubber was so cheap that there was every stimulus to find new uses for it. The chlorinated rubber is much less active chemically than ordinary rubber; indeed, it is so inert that it is extraordinarily resistant to both strong acids and strong alkalis, and this unique property makes it very valuable as a protective coating for apparatus exposed to attack by strong chemicals.

All this work on the structure of big molecules is not only of academic interest; it influences us all in our everyday life. Bread and paper, silk stockings and motor tyres—they are

all largely made up of these condensed giant molecules. The new moulding materials are finding ever wider uses in tableware, in electric fittings, in ornamental containers, and in countless other familiar articles. It is now hundreds of millions of years since nature in her unsystematic, empirical way discovered the possibilities of the giant molecule as a means of putting old materials to new uses. Man in his turn has gradually become aware that these condensed and polymerized substances, untractable though they may at first sight seem to be, will yield up their secrets to patient investigation, and that as they become better understood their properties can be predicted and controlled with ever greater precision. This new branch of chemistry is not only of importance to the philosopher, studying the architecture of living things, but, what may seem of much more importance to many of us, it has helped to make the world a more attractive place to live in.

CHAPTER VII

STEPPING-STONES

WE have already obtained some idea of the extremely complicated structures which the living cell is able to build up. Many of those triumphs of molecular architecture are quite beyond the synthetic resources of even the most skilful organic chemist of to-day. In the case of many of the simpler natural products, the laboratory chemist has succeeded in imitating nature in as far as he has been able to build them up from simple substances and ultimately from the elements. Every year the list of natural products so synthesized in the laboratory increases both in number and variety. Alkaloids and other plant products of toxic and medicinal power, oils and essences of various kinds, the substances responsible for the smell of the civet cat and for the odour of violets, the colouring matters of the flowers of the geranium and the rose—all these and many others have been produced within the flasks and test-tubes of the organic chemist. Even haemin, the characteristic iron-containing structure present in haemoglobin in combination with a protein, has been synthesized in the laboratory. But the majority of compounds which are constantly being formed in the living cell are still outside the range of the chemist's technique. How are they produced?

The problem appears all the more remarkable when we think of the conditions under which the living cell works. The organic chemist has at his disposal a whole series of powerful reagents—concentrated acids and alkalis, compounds of high chemical reactivity such as aluminium chloride and phosphorus pentachloride—and, this is most important, he is able to control the temperature at which his reactions take place. He can keep his substances, should he wish, far below the freezing-point of water—when necessary in the neighbourhood of

absolute zero—or he can pass them through red-hot tubes. But in spite of this great control of the experimental conditions and in spite of his unceasing attempts to improve his methods, he is often unable to avoid the formation of many useless by-products and his yield of the desired compound may correspond to only a very small fraction of his starting-out material.

The living cell, on the other hand, must perforce carry out all its reactions at a constant temperature or at one which varies only within narrow limits. Furthermore, with a few exceptions, the medium within which these reactions are carried out is nearly neutral. Strongly acid and strongly alkaline solutions are equally excluded. Yet in many cases the yield of the desired compound is very high, and where by-products are produced they are usually limited to such as can be utilized for some other purpose. Thus the whole chemistry of the living cell is of a smoother, more efficient, more elegant type than that to which we are accustomed in our beakers and test-tubes. What secrets do the animals and plants possess which make it possible for them to carry out these feats of chemical technique?

Not only does the chemist fail to copy nature's elegant synthetic methods, but even the far simpler task of breaking up complex molecules into their component parts is one for which nature's methods are much more efficient than his. If the chemist wants to hydrolyse starch into sugar, he can do no better than to boil it for an hour or so with hydrochloric acid. Compare with this the impressive rapidity with which a drop of saliva will bring about this fission of the starch molecule at body temperature. In a minute or two the starch no longer gives its characteristic blue colour when tested with iodine; within ten minutes the sweet taste of sugar is obvious. The reader will remember that the saliva, so far from being helped in its work by high temperature, is rendered inactive by the application of heat. There is evidently present in fresh saliva some "thermo-labile" reagent which brings about the

conversion of starch into sugar, a process which in ordinary neutral solution would take years to accomplish. This agent is one of the most easily demonstrated of a large class of substances which are called enzymes. These extraordinary substances may be likened to lubricants in a machine. They do not supply energy, nor in any sense do they drive the reaction, but they make its course very much easier than it would otherwise be.

It may be said that practically all chemical processes which take place in living tissues depend on the presence of enzymes. There is one large group of these agents concerned in reactions involving splitting up of large molecules such as carbohydrates, proteins, and fats into their constituent parts. Some of these enzymes under other conditions are also able to facilitate the converse reactions, the synthesis of such compounds from their constituent units, and such agents are evidently of great importance in the synthetic activities of the living cell. Another large group of enzymes is concerned with the various processes of adding or removing hydrogen and oxygen. Other enzymes are concerned with more specialized reactions, such as the removal of a carboxyl group from an organic acid. In fact, the number of enzymes is amazingly large, and many of them are highly specific not only in respect of the type of the reaction which they facilitate, but even in respect of the particular compounds on which they are able to act.

We have to imagine the whole mass of chemical activity which is so characteristic of the living cell as being governed and guided at every point by these innumerable and ubiquitous enzymes, each one present exactly where it is wanted and just in the right amount. Frequently it is a question of building up a complex substance out of its component parts or of carrying out a long series of reactions. For this purpose we must imagine the enzymes to be arranged in the right order so that each one comes into action at the exact point at which it is required, just as in the mass production of motor-cars each worker does his little part in its construction and the car

then passes on. When we remember that minute bodies like bacteria must contain many such enzyme systems, all localized in space and separated from each other, we realize how extraordinarily intricate and subtle the structure of the living cell must be.

Clearly, if we could synthesize enzymes at will, industry would be revolutionized as a result of the ease with which operations, at present laborious and expensive, could be performed. But the first step towards this end is to discover what an enzyme really is, to elucidate its exact chemical structure. Already a promising beginning has been made in this direction, though the difficulties are great. Even attempts to obtain enzymes in a pure form have encountered serious obstacles. These mysterious substances are so active that very small amounts are able to promote reactions on quite a large scale. Consequently, the actual quantities present in the cells of animals or plants is usually extraordinarily small, and the result is that it is a matter of extreme difficulty to obtain reasonable quantities of an enzyme for the purpose of chemical manipulation. The trouble is all the greater because enzymes prove, in many instances at least, to be protein-like in character, and, as we have already seen, the chemical investigation of proteins, with their large and often highly sensitive molecules, is one of the most formidable tasks which the organic chemist can undertake. In recent years, however, much work has been done in this field, some of it of a novel and interesting nature, and some real progress has been made.

The ordinary methods of purifying an organic compound involve principally the processes of distillation and crystallization. The former is evidently inapplicable to unstable solids like proteins or enzymes. The latter appeared to be equally useless, for, as obtained in cell extracts or body fluids, the active agents are always associated with an overwhelming amount of inert protein, from which it seemed hopeless to expect them to crystallize out. Add to this the fact that the enzymes are very readily inactivated by heat and also by

strong acids and alkalis and by many other chemical reagents, and it will be realized that the available methods of procedure were very inadequate.

Clearly a new technique was called for, and it was the famous Richard Willstätter, then Professor at Munich University, who was the pioneer in this field. He made use of the fact that enzymes are very readily concentrated at certain surfaces. Thus, if to a solution containing an enzyme a suitable finely divided powder is added, for example, china clay, the enzyme may be taken up—or, as we say, "adsorbed" —on the surface of the particles. The clay may then be filtered or centrifuged off and the enzyme extracted from it by washing it well with a suitable solution such as one of sodium carbonate or phosphate. Naturally repetition of this double process of "adsorption" and "elution" increases the purity of the product, and it is often advantageous to change the adsorbing powder, on the principle that the impurities let through by one may be held back by another.

The development of a new technique in science is frequently the prelude to an advance in knowledge often extending into departments more or less remote from the original subject. Thus the invention of methods of producing high vacua led to the knowledge of X-rays, and so to all the remarkable advances in physics and chemistry that have ensued. The results of the development of the adsorption technique have not been so spectacular, but nevertheless, Willstätter's work on this subject has proved important in many fields outside enzyme chemistry. Thus the adsorption technique has been applied in the purification of other biochemical products, such as toxins and antitoxins and hormones, where the conditions of the problem are somewhat similar.

But the method has proved of use even in organic chemistry itself. It is the basis of the technique known as "chromatographic analysis", by means of which it has been possible to separate in a pure state various compounds previously only obtainable in association with closely related compounds of

very similar properties. This method has made it possible to separate carotene, the red pigment of carrots, into three different compounds (see p. 190); similarly, it was only through its aid that certain constituents of coal-tar were ultimately obtained in a pure state.

By the use of the method of adsorption Willstätter and his co-workers were able to separate enzymes from much of the inert material usually associated with them, and so obtain them in a relatively concentrated form. Furthermore, they observed that different enzymes, even though they might be closely related in their action, were often adsorbed more or less specifically on particular adsorbents. They could thus be separated from each other, and so the behaviour of various single enzymes could be studied under well-defined conditions. It also became possible to use these purified enzymes as tools for analytical investigations on other substances. Thus, if a certain purified enzyme preparation, known to attack one particular type of linkage only, is found to act on some compound, we can conclude that the latter contains that particular linkage.

But if enzymes can be employed as analytical tools, may they not prove of great value for synthetic purposes as well? Already certain compounds (such as hexose-phosphoric acid and creatine-phosphoric acid) are best prepared in the laboratory by the use of suitable enzyme-containing extracts, derived from yeast cells or muscle-tissue. A day may come when a large stock of enzymes of various kinds will be available commercially, so that the chemist of the future may be able to abandon the drastic and cumbersome methods upon which at present he is often forced to rely.

Though the adsorption technique led to many positive results, it did not succeed in its main object—the separation of an enzyme in a completely pure and if possible crystalline form. Some workers, indeed, were doubtful whether these agents really consisted of ordinary chemical molecules at all. Yet, if not molecules, it was clearly desirable at least to retain

the idea of characteristic atomic patterns, for otherwise how could the remarkable specificity of these agents be explained? In these circumstances the theory put forward by Willstätter had a wide appeal. According to this, enzymes consist essentially of active groups borne on large particles present in colloidal solution. These latter, called the enzyme "carriers", though facilitating the enzymatic activity in virtue of their surface forces, are themselves non-specific, and the specificity is regarded as being dependent on the special active groups.

And then, just when most people seemed inclined to accept this theory, a very unexpected and embarrassing thing happened. Dr. Sumner, an American biochemist, was working with a highly active preparation of urease, which he happened to set aside in the ice-chest. (Urease is an enzyme which converts urea into ammonium carbonate. As it does this rapidly and completely, and the ammonia formed is easily measured, it is very much used in laboratories for the purpose of estimating urea in blood and urine.) Dr. Sumner's preparation deposited crystals which were evidently protein in nature. When filtered off and examined these crystals proved to possess the characteristic enzyme activity of the original solution. The most obvious conclusion was that they were simple crystals of an inactive protein with small quantities of an intensely active enzyme adsorbed on their surfaces. However, by careful experimentation Sumner convinced himself that this hypothesis was not the correct one and that the crystalline material was nothing else than the enzyme itself. Apparently he had obtained urease in a crystalline form. Naturally, biochemical opinion was very sceptical, not to say incredulous. The result seemed too good to be true. Besides, similar claims had been made in the past and had failed to withstand criticism. However, it soon became clear that Sumner's conclusions could not be lightly rejected. This was especially so when other crystalline enzymes began to appear in various laboratories. For example, Northrop, working in the Rockefeller Institute in New York, reported that he had

succeeded in crystallizing pepsin, the enzyme present in the gastric juice which brings about the first stage in the digestion of protein. Subsequently he succeeded in obtaining certain other digestive enzymes in a crystalline form, including trypsin, the protein-splitting agent of the pancreatic secretion.

Nowadays, the crystallization of an enzyme has become almost a commonplace. Once the chemist realized that enzymes might be crystallized, and had learned some of the tricks promoting crystallization, the list of crystalline enzymes soon began to extend. Scarcely a year passed without a few being added. Some continue to resist strenuous attempts to crystallize them; whether this is due to some inherent feature of their structure, or perhaps to the fact that they are especially highly active, so that it is very difficult to obtain any workable amount of enzyme and separate it from a relatively very large quantity of associated inert material, still remains doubtful. In any case, crystalline enzymes are now accepted even by the most conservative of biochemists.

In the mouth and alimentary tract, we meet with enzymes whose function it is to break up the complicated molecules present in the food so as to make them suitable for absorption into the body proper; for the alimentary tract, although geometrically within the body, is no more part of the body than a tunnel is part of the mountain through which it passes. The constituent units into which the food is broken up in the alimentary tract have to be utilized in the tissues of the body, and some of them are built up into the complicated molecules such as protein and glycogen, which are necessary for the proper structure and behaviour of the body. The enzymes in the tissues must therefore be able to build up as well as break down.

It happens that it is in connexion with glycogen and starch that our knowledge of how the living cell builds up a complicated molecule is most complete. The story begins in 1936 when Carl F. Cori and his wife, Gertie T. Cori, who had for many years made a special study of carbohydrate metabolism,

found that in frog muscle there was an enzyme which in the presence of inorganic phosphate split up glycogen in a novel way. Amylase, as we have said, produces maltose, but the new enzyme caused the glucose units to break off separately, each in combination with a molecule of phosphoric acid. The product was a hitherto unknown combination of glucose and phosphoric acid, often called the Cori ester, and possessing the formal name of glucose-1-phosphate. Similar enzymes, to all of which the name "phosphorylase" has been given, are found in yeast cells, in muscle, in heart, and in various plant tissues, such as potato tubers and ungerminated peas. All these phosphorylases act on starch as well as on glycogen.

When amylase acts on starch-producing maltose, a good deal of energy is liberated as heat. When Cori ester is formed under the influence of phosphorylase, a similar liberation of heat does not take place; the energy which would otherwise be liberated by the fission of the links joining the glucose units together in the starch is now stored up in the bond joining the glucose to the phosphate. It is no longer lost, dissipated as heat. It is there in the ester molecule, available if required for re-forming the glucose-glucose links and so rebuilding the polysaccharide. We can see how it is possible for a reaction of this kind, where there is no serious loss of energy to be capable of easy reversal. In fact, it was found that phosphorylase acts on the Cori ester, producing a glycogen-like compound, and at the same time liberating phosphate. Almost simultaneously Kiessling in Germany, working with yeast phosphorylase, the Coris in America with muscle phosphorylase, and Hanes in Britain with the phosphorylase of peas and potato tubers, found that according to the conditions the reaction went in one direction or the other. Starting with the Cori ester, the enzyme produced polysaccharide and phosphate, starting with polysaccharide and phosphate, it produced Cori ester.

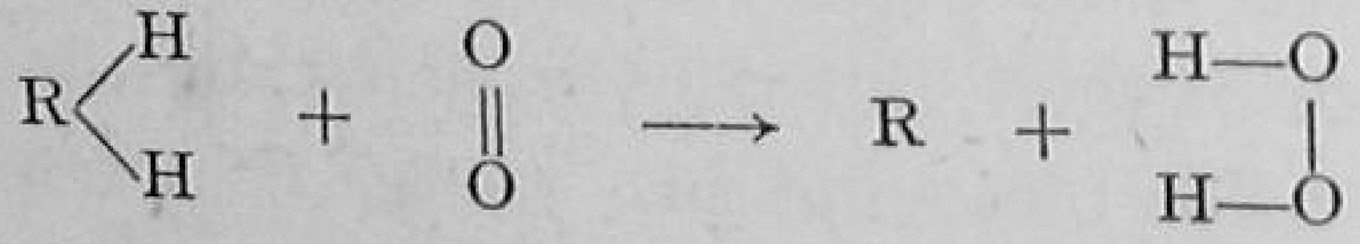
In 1942, the Coris and their colleagues succeeded in obtaining muscle phosphorylase in a crystalline state; phosphorylases

from other sources have been purified, but not yet crystallized. Phosphorylase is not the only enzyme concerned in the synthesis of glycogen and starch. The fact is, crystalline phosphorylase, acting on Cori ester, does not synthesize either of these two natural products: it synthesizes a substance called amylose which is present in ordinary starch to the extent of some 20 per cent and is largely responsible for its power when dissolved in water to form a jelly. The other constituent of starch, amylopectin, required a second enzyme for its formation. This second enzyme is present in potato tubers, and acts on amylose, either the natural or synthetic variety, to convert it into the more complicated amylopectin. By means, then, of these two enzymes, starch, a really complicated natural product, comparable in complexity to the proteins, has been synthesized by the chemist without making direct use of any living organism. This achievement has revealed to us something of nature's synthetic methods, and shows us how effectively an enzyme can build up as well as break down.

As we have just seen, the synthesis of starch from the Cori ester requires the help of two enzymes. This is a relatively simple example; often the most seemingly simple reaction requires the assistance of quite a number of these agents. Take the example, very important in biology, of the oxidation of an organic compound by oxygen. This is the fundamental reaction from which we derive our energy and body heat; our cells are constantly oxidizing carbohydrates, fats, and proteins. Oddly enough, the reaction which the organic compound undergoes in the first place is not usually oxidation proper, the addition of oxygen, but dehydrogenation, the removal of hydrogen. If after removing two atoms of hydrogen we add on a molecule of water, the net result is to add on one atom of oxygen. Now the addition or removal of a molecule of water from an organic compound is often a relatively easy process and so dehydrogenation and oxidation are virtually equivalent. The chemist has been led to appreciate that dehydrogenation is the essence of most of the processes of

oxidation on which so many living cells depend. Under the control of appropriate enzyme systems the hydrogen atoms are removed and in due course combine with an atom of oxygen to form a molecule of water. The details of this apparently simple operation are in practice usually rather complicated. They depend to some extent on the nature of the compound supplying the hydrogen atoms and also probably on the nature of the tissue within which the reaction takes place. One of the earliest examples of this kind of system to be worked out in detail concerned the oxidation of a phosphoric ester of glucose, not the Cori ester already mentioned, but a very closely related one—glucose-6-phosphate. These two esters are converted each into the other by an enzyme present in the tissues called by the awkward but self-explanatory name phosphoglucomutase; in presence of this enzyme a mixture of the two esters exists in definite proportions. But this is by the way; let us attend to the oxidation of the glucose-6-phosphate. This was first studied by Professor Otto Warburg and his assistants in his institute at Dahlem, Berlin. Warburg worked on this enzyme system as obtained from the red blood cells of the horse—a very convenient source.

The effect of this system is to transfer two atoms of hydrogen from each molecule of glucose-6-phosphoric acid to an atom of oxygen; the acid thereby becomes phospho-hexonic acid, whilst in place of the oxygen we have hydrogen peroxide. Denoting phospho-hexonic acid by R and glucose-6-phosphoric acid by RH_2 we may represent the reaction as follows:



This seems a very simple process, yet left to their own resources, in the absence of the enzyme system, the two atoms completely fail to transfer themselves from the one molecule to the other. We may think of them as two travellers trying to get across a river too wide for them to jump. An obvious

device, in the absence of a bridge, is to make use of stepping-stones. The enzyme system, in fact, provides two such stepping-stones, which we may call A and B. The two hydrogen atoms jump from the original acid RH_2 to the first stepping-stone A, then from A to B, and finally from B to the oxygen molecule forming hydrogen peroxide. This device of carrying out a difficult reaction in a relatively large number of quite small stages is indeed characteristic of many processes of the living cell. The enzyme system which we are at present considering is only a special case of this general principle.

So far, we have regarded the hydrogen atoms alone as the travellers hastening across the river to unite with their partners, the oxygen molecules on the other side. This indeed corresponds to what happens in many laboratory experiments with these enzyme systems; but in the body it is rather different. In living tissues the oxygen is not relatively abundant, as it is in the atmosphere, but exists only at a much lower pressure, so that the hydrogen atoms would have difficulty in finding partners even after they reached the opposite bank. Something has to be done to help on the reaction. What happens is that the oxygen atoms are encouraged to meet the hydrogen half-way by the provision of a second series of stepping-stones from their own bank of the river, and we may imagine the two lots of atoms, hydrogen and oxygen, meeting on an island in the middle (Fig. 22). Biologically, this has a further great advantage: the oxygen comes along its stepping-stones not in the form of molecules, but as atoms. Now a single atom unites with the hydrogen to form water, whereas a molecule of oxygen picking up its hydrogen, tends rather, as we said above, to produce hydrogen peroxide, which is poisonous and so avoided by nature wherever possible.

But the stepping-stones do not represent the whole story of this enzyme system. By themselves they are scarcely sufficient to bridge the gap between the hexose-phosphoric acid RH_2, and the oxygen. It seems, for example, that the

two gaps between RH_2 and A and between A and B are too great for hydrogen atoms to leap across unaided, and so handrails have to be provided to help them over. These handrails take the form of two special proteins which we may call *a* and *b*. The protein *a* helps the hydrogen atoms from RH_2 to A, whilst *b* comes into action at the next stage.

These two proteins which play the part of handrails may be regarded as simple elementary enzymes, comparable with pepsin or urease. We do not know how they work, but it

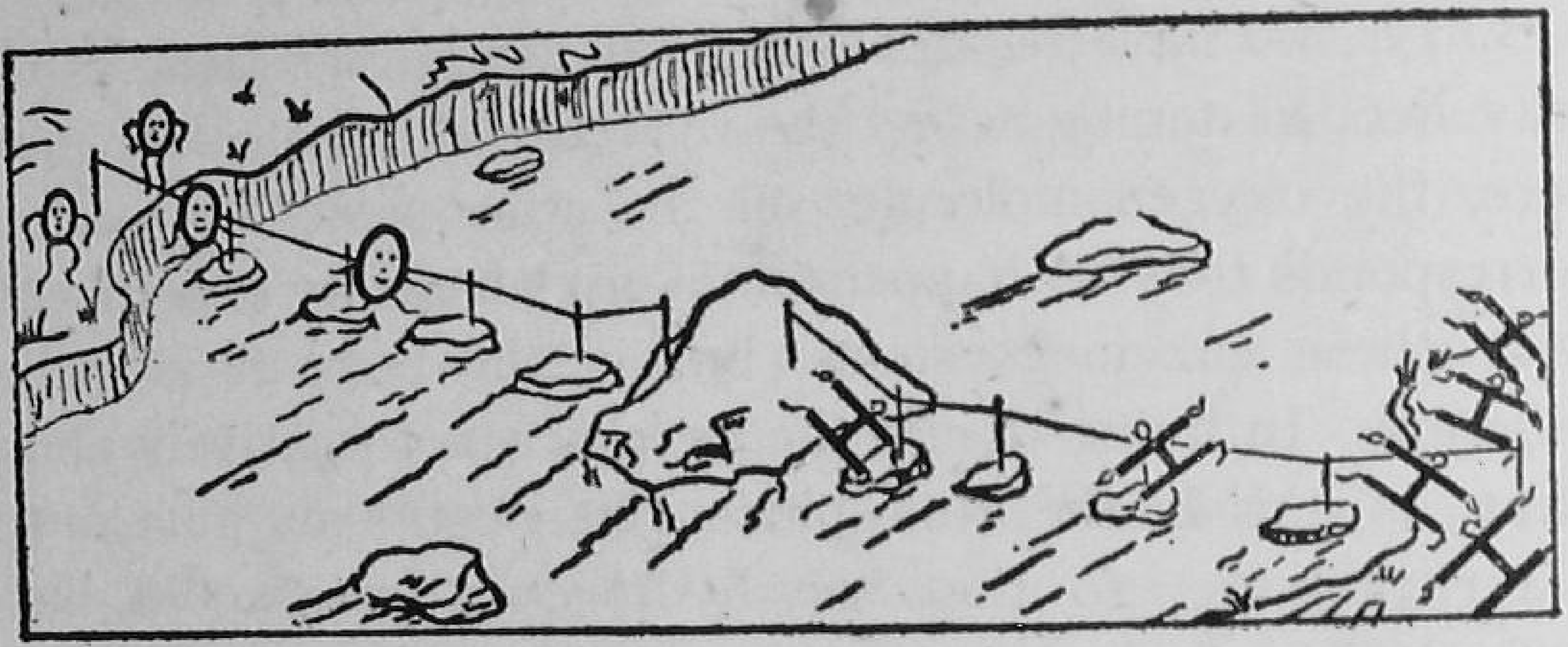


FIG. 22.—Illustrating some of the molecular stepping-stones present in living tissues. The hydrogen and oxygen atoms, separated by an otherwise formidable barrier, are enabled by the use of stepping-stones (co-enzymes) and the handrails (apoenzymes) to move towards each other and ultimately unite to form molecules of H_2O.

does seem that they form some sort of union, though not a completely fast one, with their respective stepping-stones. Indeed, one of the first big advances in all this work was the isolation by Warburg and Christian of a substance which they called the "yellow oxidation enzyme". This has proved to be a combination of B and *b*—it can be dissociated into its two components, neither of which separately suffices to make the enzyme system work as a whole, but which can be made to recombine into the original active substance. In the case of *a* and A the union does not appear to be so intimate a one, and the two components are readily isolated as two separate and distinct substances.

And now let us inquire of what the "stepping-stones" really

consist. Those used by the oxygen seem to be somewhat complicated, but one of them is an iron-containing compound generally called "cytochrome". The chemical constitution of cytochrome and its special relation to haemoglobin and chlorophyll will be referred to in a later chapter (see p. 278). It is sufficient here to remark that it is the iron atom in the cytochrome molecule upon which the oxygen alights, the iron assuming the trivalent state and reverting to the divalent form when the oxygen leaves it.

Nicotinic acid   Amide of nicotinic acid

FIG. 23.

The hydrogen stepping-stone B proves to be nothing else but riboflavin (vitamin B_2, see p. 270) combined with phosphoric acid. Here we have some indication of the role played by this particular vitamin in the animal organism. This was a very interesting discovery, for it was the first case in which we were able to assign an exact chemical function to a vitamin —a function readily understood in terms of its structure. The significance of this result is evident when it is remembered that riboflavine is widely distributed in animal tissues, so that it would seem to be of quite general importance in biological oxidations.

The hydrogen stepping-stone A proves to be a somewhat complicated molecule called the "hydrogen transporting co-enzyme" or "codehydrogenase II". On hydrolysis it yields a nitrogenous substance called adenine along with phosphoric acid, a sugar, and—most interesting of all—a second nitrogenous compound which was identified as the amide of nicotinic acid (see Fig. 23). The occurrence of this last compound as an important constituent of living matter was entirely unsuspected. Nicotinic acid was previously known

merely as a product of the oxidation of nicotine in the laboratory, but now its amide proves to be the active group in the "hydrogen transporting co-enzyme". It is on this that the two hydrogen atoms actually land in their passage from RH_2 to the oxygen.

Nicotinic acid amide has also been shown to be an essential constituent of another very closely related stepping-stone found in many animal cells and also in yeast, called "co-dehydrogenase I" or, more familiarly, "cozymase", because it was first encountered in connexion with fermentation (Gr. Zyme, leaven). It looks as if nicotinic acid or its amide were essential to most living cells (see p. 210).

We have had occasion to refer to examples of three different types of enzymes: some are concerned with the reactions of the phosphate group, such as phosphorylase and phosphoglucomutase; others promote the addition or removal of water, and here we may include the hydrolytic enzymes; and still others bring about dehydrogenation and oxidation. There are many other types to be found even in a single living cell. From yeast alone dozens of enzymes have been obtained, and there are doubtless plenty more still to come. These enzymes may be thought of as the players in a vast orchestra; each controls his own instrument and so makes his own small contribution to the musical performance, which is the whole metabolism of the living cell. But where is the conductor, controlling the innumerable performers? He is not easily to be identified; what we have seems really to be a vast swing orchestra performing a jam session. Each player is guided not by any centrally placed conductor, but by the actual music as it reaches his ears. He may glance round and receive a special signal now and then from his neighbours; he himself may sometimes send instructions to them; clearly innumerable delicate relationships must exist between all the players if the musical performance is to be harmonious and efficient.

In a higher animal or plant, of course, this metabolic orchestra of the single cell cannot play any tune it pleases.

Its efforts must be co-ordinated with those of its neighbours, and all must be so organized that the organism as a whole, containing millions or billions of separate cells, can assimilate food and grow and reproduce and perform all the functions incidental to these activities. This involves controls between the cells: messages have to be sent from one part of the body to the other, a central depot has to be established through which the general harmony and co-ordination of the organism can be maintained. But all this elaborate system depends on the proper functioning of the individual cells. Each has to respond correctly when the signal is given. The separate orchestras must play the right tune at the right time. We can scarcely hope fully to understand how this extraordinary feat of organization is accomplished. Within the orchestra, the best we can do is perhaps to concentrate our attention on one theme and see how this is bandied about from instrument to instrument, remembering that this is only one element out of the whole complicated performance.

The theme we shall select is that of the phosphate group. We have already met this group in connexion with the synthesis of starch. We have seen how under the influence of phosphorylase, starch or glycogen is converted into the Cori ester, glucose-1-phosphate. We have also remarked that under the influence of another enzyme, the Cori ester changes into glucose-6-phosphate.

From this point onward it would scarcely be profitable here to give a detailed account of the development of the phosphate motif. We shall only try to indicate the broad idea. In general terms we have the phosphate group united to a sugar molecule, and in the course of a complicated series of chemical reactions, all of them promoted and controlled by enzymes, the sugar is broken up in such a way as to liberate energy. Now in normal circumstances, if the phosphate group were not attached to the sugar molecule, the energy would be lost in the form of heat. But matters are so arranged that a rather curious and ingenious thing happens. The energy is not lost,

but is stored in the chemical bond by means of which the phosphate group is attached to the degraded sugar molecule. This "high-energy" phosphate bond ("high-energy P") would, of course, liberate a good deal of heat if it were simply ruptured, but naturally this wasteful course is avoided. Instead, the phosphate group, along with its special high-energy bond, is transferred to a special sort of stepping-stone, a stepping-stone which, as we shall see, occupies a very central position in the whole metabolism of the cell.

This stepping-stone is called adenylic acid, and it consists of a nitrogenous substance called adenine, a sugar called ribose, with which we are already familiar, and some phosphoric acid. It is an interesting illustration of the close connexion between the various separate reactions which go on in the cell that the two stepping-stones already mentioned in connexion with dehydrogenation contain adenylic acid as a constituent part. We are now concerned, however, with free adenylic acid, and this functioning as a stepping-stone, takes on first one and then a second extra phosphate group. It is the second of these extra phosphate groups which can be passed on easily with its bundle of energy wherever it is wanted. Sometimes it is passed on to the contractile muscle tissue, so that the energy may be available for muscle contraction and the doing of mechanical work. Sometimes it is employed to bring about the phosphorylation of a free sugar molecule, as, for example, in yeast when it ferments glucose, for here the first stage is to produce the hexose-6-phosphate, from which the process of cell fermentation starts.

There are many other uses to which the "high-energy P" is put—the phosphate stepping-stone, in fact, is a centre with many connexions to key points in the network of metabolic reactions. But being a major traffic centre, it is apt to become congested—or rather it would be, if it were not associated with a special storage device. The excess of "high-energy P" it can transfer to a second stepping-stone, an ancillary stone, rather roomier than itself and connected to it by an easy

two-way bridge. This islet is the rather simple, nitrogenous substance known as creatine; we shall have more to say about it and the combination with phosphate, phospho-creatine, in a subsequent chapter. This special store of "high-energy P" is immediately available to replenish the adenylic acid stepping-stone whenever it has been suddenly depleted, as, for example, during muscular contraction. The main supply from the sugar-phosphate system is too slow to deal with such sudden demands, but, of course, when the need is there it is speeded up and the store is ultimately replenished.

There must be a score or two of known reactions centring round the phosphate group; no doubt many more still await discovery. Very few, if any, of these reactions would proceed at a reasonable rate under the conditions present in the cell in the absence of the appropriate enzymes. These agents not only cause the separate reactions to go; by being present in the right amounts and with the right degree of activity they control each reaction so that it just goes at the proper rate and thus ensure that the whole cell metabolism proceeds uniformly and harmoniously. The whole mechanism must be self-regulating; clearly the activity of the enzymes themselves must be controlled by the actual conditions prevailing in the cell; just as the regulator of a thermostat is controlled by the state of affairs, the temperature, within the oven. And as we have already said, the whole complicated machinery within any one cell must be under effective external control and function in harmonious co-operation with all the other cells of the organism.

It will quite obviously be a long time before man's chemistry is able to give a reasonably complete account of even the simplest of living organisms. Nature is far ahead of us in her methods and her achievements. But it must be remembered that she has had an enormous start. The cockroach can do things quite beyond our laboratory technique, but, of course, the cockroach has been at it for millions of years and his ancestors had been experimenting for hundreds of times as

long. The organic chemistry of man was scarcely born one hundred years ago. The cockroach had an enormous start, but even already the chemist has appreciably reduced the lead, and it would be rash to set any limit to what he may some day achieve. Man is yet but a child on the earth.

However, being still a child and a young one at that, he is not yet much beyond the stage of learning his alphabet. Occasionally he is able to make out two or three consecutive letters and to recognize a small word or a syllable or two of a larger one. Sometimes he may even be able to read a small simple sentence, and then he feels very pleased with himself and begins to look forward to the time when he will be reading or even writing whole books. But at present the deciphering of a little phrase here or there gives him great pleasure. Here, for example, is an interesting fragment recently unravelled in the intricate story of development. It concerns the processes which occur in the germination of seed.

In the malting of barley, which is so important in the brewing industry, the essential factor, from a practical point of view, is the development of enzymes which convert the starch into sugar. But where do these enzymes come from? Do they exist in the barley before germination or are they synthesized *de novo* in the sprouting seed? Both alternatives would seem to present difficulties, for if the first possibility is the fact, then how does the seed manage to protect its starch from premature attack? On the second hypothesis, the freshly developing seed would have to prepare its enzymes before doing anything else, and this would seem to be asking too much even for living cells. The difficulty is overcome in an ingenious way. Recent work shows that barley contains two starch-splitting enzymes. The first, *a*, attacks the large starch molecule and splits it into a number of fragments. The second, *b*, cannot act on the intact starch granules, and only slowly on the starch molecules, but it readily attacks the fragments produced by *a*. However, in the barley extracts the first enzyme *a* is in an inactive form and so even although *b* is

active, the starch is immune from attack. In order to activate *a* it is necessary to add an activator to the system. Actually this activator appears to be a protein decomposition product, and it is formed in the germinating barley by the action of protein-splitting enzymes on the proteins which are present. Once the activator is available in the germinating grain, the *a* enzyme soon does its essential work of splitting up the starch molecules into small fragments, and these are rapidly broken down into sugar by the *b* enzyme which is present in ample amounts.

The *b* enzyme requires no activator, but it cannot operate prematurely as it must wait until the *a* one has done its preparatory work. Thus, in the germination of barley—and something similar presumably takes place in the case of other seeds as well—the protein-splitting enzymes first become active, no doubt as the result of some change in the physico-chemical conditions not yet completely elucidated. Then the rest follows automatically—the fission of the proteins, the production of the activator, the splitting up of the starch molecules, and finally the erosion and disintegration of starch granules and finally the breaking down of the starch molecules into sugar. By a simple device the plant ensures that the liberation of the stores of carbohydrate in the seed will take place just at the right moment—a short time after the proteins have begun to rearrange themselves so as to build up the structure of the growing embryo.

In this way, then, has one short sentence—or perhaps only a minor phrase—in the complex story of the development of living organisms been deciphered. A number of such isolated fragments have been made out. So far they are, in general, still unconnected words and phrases, but familiarity with them makes it possible to recognize similar constructions elsewhere. As knowledge and experience increase and new methods become available, we may hope to be able to piece the disjointed fragments together, and so to obtain some notion of the main threads of the story running through the book of life.

CHAPTER VIII

ENGINES AND ENERGY

EVER since the time when man first become a self-conscious, thinking animal he must have been painfully aware of the need to exert energy in order to get things done. At the early stages of his development he was practically entirely dependent on man-power for the achievement of his aims: either on his own muscular energy, or on the muscular energy of others over whom he had control. By the domestication of animals, by the harnessing of the forces of wind and water, man through the ages has tapped an ever-increasing number of energy sources to help out his own strength; and to-day, with the discovery of the internal combustion engine, the steam turbine, and the dynamo, so great are the resources at his command that it is no longer true—or need not be—that "in the sweat of thy face shalt thou eat bread". Yet man's body is still as it always was, a machine for getting work done.

Even from a superficial point of view it is easy to see that all these mechanical systems have at least one feature in common, the need for a supply of energy. In the case of men and animals, the power to do work is ultimately dependent on a supply of food being available. The steam engine must be fed by coal or oil and the motor-car by petrol. The wind and the streams would all cease to exist if the heat of the sun were not available. Here we have an indication of one of the most important conceptions of modern science, the idea of the permanence of energy. We cannot create energy from nothing; an engine can only go on producing energy when suitably fed. A machine may be likened to a bank: you may pay in cheques and draw out pound-notes or coins, or you may pay in the coins and draw cheques; but what you draw out must not exceed in value what you pay in, although the

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form may be quite different. In the same way, the steam engine, fed by heat derived from the combustion of coal, may give out part of this energy in the form of the mechanical energy of an express train, and the rest as wasted heat.

And what exactly, we may ask, is energy? The practical man might answer that it is what enables work to be done. But this is rather like explaining sugar as being that with which we can make toffee; it does not really take us very much further. The significant thing about energy is just the fact of its permanence, the fact that it is indestructible. As we look around us, the superficially attractive things, the exciting things, are those which move and change, and present us ever with something new; but it is the things which are most permanent which in the end we think most real.

Now in any material system so isolated as to be entirely uninfluenced by the rest of the universe, there are certain features which possess this quality of permanence. One of the simplest and best known of these is the mass; every student of chemistry early meets the fundamental law that the mass of the system is conserved in any chemical reaction. It happens that we can measure mass—or, at least, weight, which is proportional to it—very easily with the aid of a balance, and so we imagine we have some understanding of it.

Now, if we know the position and velocities of all the particles in a mechanical system, we find we can calculate from them a certain rather complicated quantity, which in spite of all the changes in the individual positions and velocities has the peculiarity that it, too, remains constant—like mass, it is conserved. The existence of this quantity is a consequence of the laws of motion. If we do not restrict ourselves to simple dynamical systems, but include electricity and magnetism and undulatory motion such as light, we find the fundamental principle remains true—a quantity can always be calculated which stays constant whatever else may change. It happens that there is no simple general method of measuring this quantity directly. We can always estimate it, but only by

roundabout calculations. Its permanence is therefore not directly obvious, and so it seems to us rather abstract. But from the physical point of view, permanence, however established, is the very essence of reality. We give the quantity we so calculate a name: we call it energy. We can then state the result that the total energy in an isolated physical system remains constant, and we can think of energy as something rather like an indestructible fluid, which can be transferred from one system to another, but which never changes in total amount. In this it is exactly analogous to mass; and indeed it is one of the remarkable discoveries of twentieth-century physics that energy and mass, although apparently so different—the one concrete and the other abstract—are in reality very closely related.

But the developments of physics during the twentieth century have made it clear that mass and energy are more than closely related. All energy it appears, has mass. When we are dealing with the amounts of energy ordinarily met with in everyday life, the mass involved is practically negligible. The heat liberated by burning a scuttleful of coal has a mass of about a millionth of a gramme. Such a quantity could scarcely be detected experimentally; nevertheless, strictly speaking, the principle of the conservation of mass in, say, a chemical reaction holds rigorously only when the mass of any energy lost or gained is taken into account. The energy which pours forth from the sun is so enormous that this body is actually losing mass at the rate of half a billion tons per day. Even in the laboratory, it is sometimes possible to measure the loss of mass which accompanies the emission of energy. When the quantities of energy emitted are very great in proportion to the mass of the body which emits it, the situation is favourable for obtaining a positive result. This is the case with the so-called "atomic energy"; the energy released from the nucleus of an atom may be so great that the mass of the material products of disintegration may be significantly less than the initial mass. What is conserved is the total mass,

including the mass of the energy. Material mass, in fact, may be transformed into energy, just as one kind of energy may be transformed into another. In other words, we may regard material mass as one form of energy; the principle of conservation of energy holds only when any transformation of this form is taken into account. All the various forms of energy possess mass, and so it is a short step to regard mass and energy as really one and the same thing. When this basic "thing" is tied up in the form of electrons, protons, or atomic nuclei, we find it convenient to speak of "material" mass; when it is more accessible and undergoes changes from one form to another, we normally call it energy. But conservation of mass is maintained only when the mass of the "energy" is allowed for; the correction involved is usually minute and scarcely observable, and for this reason the "conservation of mass" in the old-fashioned sense holds for all practical purposes. In calculating the total energy of a system, we normally attribute an appropriate amount of energy to the various material particles, calling it the kinetic energy of these particles; these amounts are measured from a more or less arbitrary level of particle energy, but so long as this level remains the same, the effect is simply to exclude a large but fixed amount of the mass-energy entirely from the balance sheet, and so the principle of the conservation of energy is not interfered with. In what follows, it is the readily accessible, easily transformable energy that we are concerned with.

Most of us spend quite a lot of our income every year in purchasing energy in one form or another. We buy the energy essential for our bodily activity in the form of food; we pay our coal, gas, and electricity bills in return for energy in the form of heat or light. The electricity account may also cover the price of a certain amount of mechanical work if we possess a vacuum cleaner, and even the cost of a large amount of noise if we also own a mains-driven wireless set. But, whatever the form we choose to have it in, it is essentially energy we are paying for. As in the case of many other

commodities some ways of purchasing it are more costly than others.

In order to compare the price of energy in some of its common forms, it is convenient to measure it in terms of calories. A calorie is primarily a quantity of heat, but as all energy may be converted into heat, it is quite easy to apply this unit to any form of energy whatever. Let us see how many calories we can buy for a penny; or, rather, as prices have not yet settled down, how many we could have bought in 1939.

If we got our electricity at a halfpenny a unit, we thought the price quite reasonable. We then received about one million seven hundred thousand calories, or 1,700 Kilocalories for a penny. But if we decided to have our energy in the form of coal gas at, say, 6d. per therm, we then obtained a little over four thousand Kilocalories for a penny, and paraffin at a shilling per gallon gave us about the same. It is interesting to compare with these figures the cost of calories bought as coal (see Fig. 24). If we take the price to have been £2 per ton, we find that we obtained about 15,000 Kilocalories for our penny. Coal is evidently by far the cheapest of our common sources of energy. It is easy to see why it is still our great basic source of power; it is likely to remain so until atomic energy is a practical commercial proposition.

But this comparison is not quite a fair one. If we want to drive a train, an electric locomotive will convert over 90 per cent of the energy we pay for into mechanical work, whereas the steam engine heated by coal or oil will not be able to utilize much more than a quarter of the energy available in the fuel. The rest is given off as heat and for all practical purposes is lost. Thus, if we are interested in the amount of work we can get for our penny, we must divide the figures for gas, oil, or coal by about 4, whilst that for electricity remains almost unchanged. From this point of view, coal is still cheaper than anything else, but electricity is now cheaper than paraffin and not very different from Diesel oil. Other things

being equal, it should cost less to travel by steam-train than in the tram-car, and less in the latter than in a petrol-driven vehicle. The Diesel oil engine, on the other hand, should be able to compete with electricity as a source of power, the choice depending mainly on subsidiary questions of convenience and special conditions. It is interesting to observe

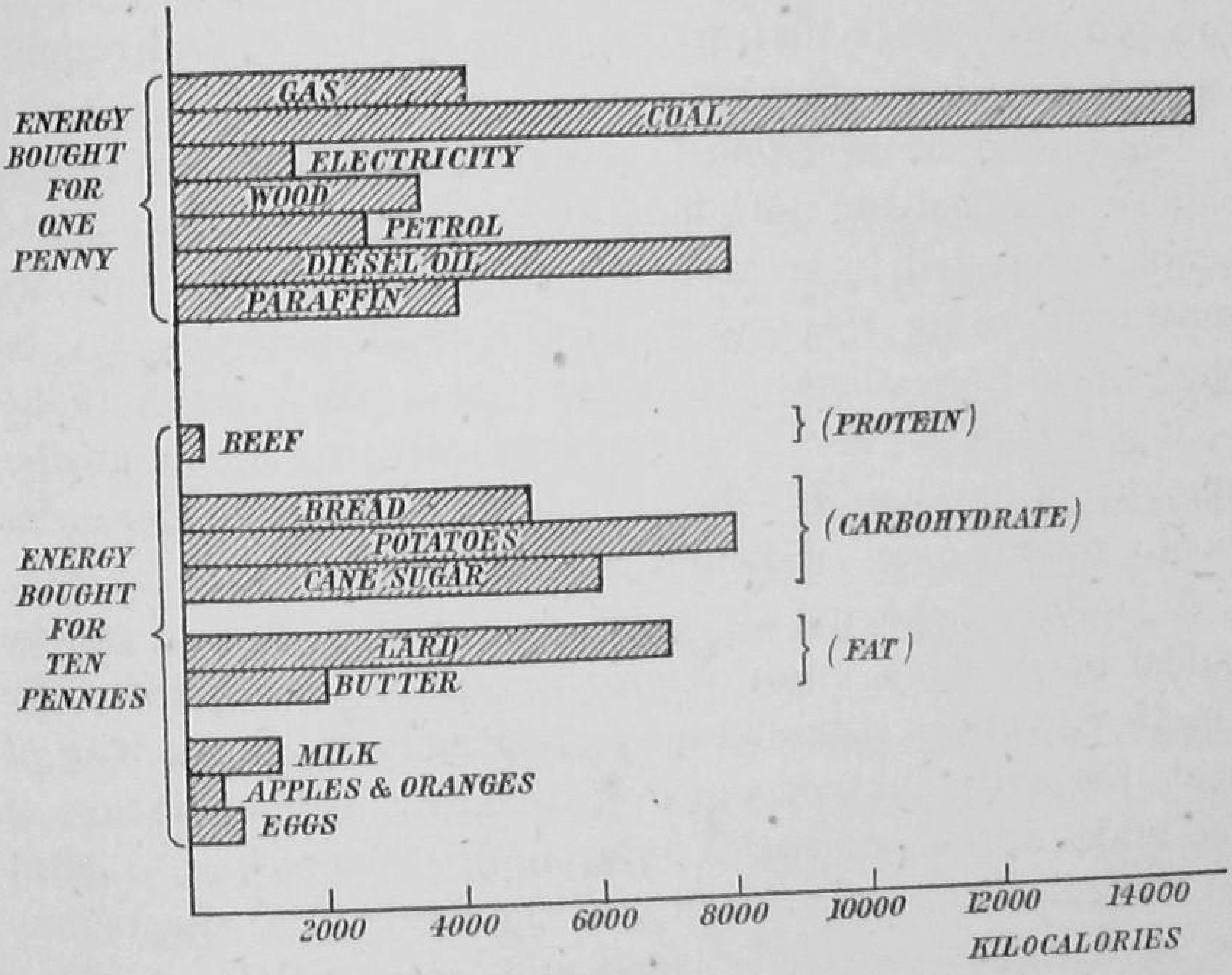

FIG. 24.—Cost of energy purchased in different forms (based on 1939 prices).

that these two sources of energy are actually in keen competition, both on the roads and on the railways.

Let us now pause for a moment to consider just what a Kilocalorie of energy actually looks like. Without some notion of the units we are using it is difficult to get things into a proper perspective. If we are thinking of energy in the form of heat, then we may picture a Kilocalorie as the amount of heat needed to raise a tablespoonful of water from room temperature almost to the boil. An ordinary 75-watt bulb gives out this amount of heat in rather less than a minute.

But perhaps we are interested in mechanical energy rather than heat. In this case we can imagine a bullet weighing an ounce travelling through the air at a typical speed of 1,500 ft. per second or an athlete sprinting at rather over twenty miles per hour. In each case the energy of motion at any instant is about a Kilocalorie. Evidently a relatively trifling amount of heat is equivalent to a quantity of mechanical energy which can produce effects that are far from negligible, and require to be treated with great respect.

The amount of mechanical energy corresponding to a calorie of heat is called the "Mechanical Equivalent of Heat", and people interested in heat engines and power production are constantly using this factor in their calculations. If the Mechanical Equivalent of Heat were much less than it actually is, if one Kilocalorie of heat corresponded to a much smaller amount of mechanical energy, many ordinary experiences would assume a very different aspect.

A motor-car moving along at a speed of 30 m.p.h. can be pulled up in a few yards when the brakes are applied. The kinetic energy is converted into a relatively small quantity of heat, the only effect of which is to raise the temperature of the brake drums and bands by a hundred degrees or so. But let this car collide with a wall, and the mechanical effects may be of a most spectacular type and apparently out of all proportion to the small quantity of energy (in terms of heat) involved. It is the large mechanical equivalent of heat which makes it so easy to control mechanical energy by means of brakes and similar devices. If the mechanical equivalent were only a tenth of what it really is, all braking devices would have to be much bigger and clumsier, or else they would be melted away when they were applied.

In the same way, from the point of view of producing mechanical energy from heat it is likewise exceedingly fortunate that the mechanical equivalent should be so large. A smaller factor would mean that all heat engines would require proportionately more heat in order that a given quantity of

mechanical energy should be obtained from them, and to pass ten times as much heat into the boiler of an engine would possibly present a problem very difficult of solution. A world constructed with a *very* low mechanical equivalent of heat would show all sorts of curious phenomena. Water might start boiling when we stirred it, our skins might blister when we rubbed them, or our joints seize whenever we moved. A stone flung through the air might be melted or even volatilized by the friction, just like a meteorite passing through the atmosphere at a very much higher velocity.

Though we speak of the Mechanical Equivalent of Heat, nevertheless heat is itself in reality kinetic energy, that is, energy of movement. In a gas it is the kinetic energy of the separate molecules which constitutes the heat. These molecules are rushing about in all directions and the vast majority of them have relatively high speeds: at ordinary temperatures they move at about fifteen miles a minute. When a falling stone comes to rest on the ground, its kinetic energy is converted into heat, and this really means that the molecules of the stone and the adjacent ground vibrate backwards and forwards a little more vigorously than before. Are we then to conclude that there is no essential difference between heat and mechanical energy?

The key to the answer is to be found in the idea of random motion. In the case of the moving stone, the particles are all moving approximately parallel to each other, whereas in the case of the heated ground the movements are in all directions. Now random movements of this kind are of no direct use to us from the point of view of obtaining mechanical work. These random movements cannot be applied in any simple way so as to impart a velocity in some given direction to any particular object. On the other hand, the falling stone will tend to drive forwards any object with which it comes in contact. The difference is somewhat analogous to that between a well-drilled column of soldiers moving forward in regular formation and a mob of frightened people rushing hither and thither in

all directions. As individuals, the mob may be just as active as the soldiers, but whereas the activity of the soldiers may be readily directed to any desired object, that of the mob is uncontrollable and serves no useful purpose.

However, the case of the heat engine shows that heat is not altogether useless for performing mechanical work. Mechanical energy is completely available for any purpose whatever, whereas heat energy is only available in a limited sense; in fact, it may be said to be available only in so far as it tends to flow from one place to another. But heat only flows from points of higher temperature to points of lower temperature, so that heat energy only becomes available for mechanical work when it is stored at a higher temperature, and then made to flow into a reservoir at a lower temperature. The higher the initial and the lower the final temperatures, the greater the possible efficiency of the conversion. This is why in steam engines it is an advantage to work with "superheated" steam—steam raised in a high-pressure boiler to a temperature well over the ordinary boiling-point of water. This principle implies that there is a definite limit to the efficiency of a heat engine. However well designed it is, it will not be possible for it to convert more than a fraction of the heat supplied into work, the rest being of necessity wasted in the exhaust. This applies to steam engines of all kinds, as well as to internal combustion engines. The highest efficiencies that have so far been reached in practice are in the neighbourhood of 35 per cent.

These laws of energy apply to all material systems, however complex they may be. They apply, for example, to the systems of atoms and molecules which constitute living bodies. This is confirmed by all reliable experiments on living material as well as by general theoretical considerations. We have already explained (p. 27) how the properties of aggregates may be simpler than the properties of the individual units of which they are composed. In a somewhat analogous way, the details of the mechanical system may be very intricate, yet at the same time the system as a whole may be subject to some

quite simple and easily understood laws. For instance, if we pour water down a sink with an open exit we know it will always run out, although it would be a seriously complicated matter to trace the courses of the individual molecules and calculate their paths. Nevertheless, the water as a whole is the aggregate of all these molecules. It is similar with respect to the laws of energy as applied to the material systems which constitute living bodies.

And now, in the light of these principles, let us consider the living body as an engine for the performance of mechanical work. Fuel is supplied in the form of foodstuffs. These are digested, absorbed into the blood-stream, and carried to the tissues, where they are burnt up; that is to say, they combine with the oxygen which is also brought to the tissues by the blood-stream. The chief product is carbon dioxide, as in the case of ordinary combustion. The three main types of foodstuffs which are thus oxidized in the tissues are carbohydrates, proteins, and fats. The first two classes of substances we have already discussed, but a word might be said about the fat. This material is very nearly related to petrol or paraffin. In fact, fat may be regarded as paraffin which has been modified so as to enable it to be more easily dealt with in the watery medium of the living body (see Fig. 25):

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\begin{array}{l}
\mathrm{CH_2{-}O{-}CO{-}CH_2{-}CH_2{-}CH_2{-}CH_2{-}CH_2{-}CH_2{-}CH_2{-}CH_2{-}CH_2{-}CH_2{-}CH_2{-}CH_2{-}CH_3} \\
| \\
\mathrm{CH{-}O{-}CO{-}CH_2{-}CH_2{-}CH_2{-}CH_2{-}CH_2{-}CH_2{-}CH_2{-}CH_2{-}CH_2{-}CH_2{-}CH_2{-}CH_2{-}CH_3} \\
| \\
\mathrm{CH_2{-}O{-}CO{-}CH_2{-}CH_2{-}CH_2{-}CH_2{-}CH_2{-}CH_2{-}CH_2{-}CH_2{-}CH_2{-}CH_2{-}CH_2{-}CH_2{-}CH_3}
\end{array}
$$

One molecule of fat.

$$
\begin{array}{ll}
\mathrm{CH_3{-}CH_2{-}CH_2{-}CH_2{-}CH_2{-}CH_2{-}CH_2{-}CH_3} & \mathrm{CH_3{-}CH_2{-}CH_2{-}CH_2{-}CH_2{-}CH_2{-}CH_2{-}CH_3} \\
\mathrm{CH_3{-}CH_2{-}CH_2{-}CH_2{-}CH_2{-}CH_2{-}CH_2{-}CH_3} & \mathrm{CH_3{-}CH_2{-}CH_2{-}CH_2{-}CH_2{-}CH_2{-}CH_2{-}CH_3} \\
\mathrm{CH_3{-}CH_2{-}CH_2{-}CH_2{-}CH_2{-}CH_2{-}CH_2{-}CH_3} & \mathrm{CH_3{-}CH_2{-}CH_2{-}CH_2{-}CH_2{-}CH_2{-}CH_2{-}CH_3}
\end{array}
$$

Six molecules of octane (petrol).

FIG. 25.

It is an interesting question whether or not the animal body can be properly regarded as a *heat* engine. The essential point

about a heat engine is that the energy at one stage exists as heat at some definite temperature. Thus, in the steam engine it exists as heat within the boiler; in the internal combustion engine as the heat of the gases after the explosion. In the case of an active muscle the combustion of the carbohydrate, fat, or protein liberates energy, but does it at any stage exist completely in the form of heat? If it did, then we should expect the efficiency of muscles to be limited by the same principle which holds for heat engines. The heat generated in the muscles might, of course, exist locally for a very brief instant of time at a considerably higher temperature than the average body temperature of 37° C. The effective temperature might, in fact, be quite high and efficiencies comparable to those obtained in the case of heat engines might be expected. In point of fact, the efficiency of the muscle can reach 25–30 per cent. Although this is of the right order, it is, of course, no proof that the muscle is comparable to a heat engine.

The alternative possibility is that the energy liberated is directly transformed into mechanical energy without existing intermediately as heat. The energy of a chemical reaction is not necessarily completely available for the purpose of doing mechanical work, but it is usually much more so than an equal amount of heat. The fraction available (called the "free energy" of the reaction) does not generally differ very much from the total energy of the reaction. If the muscle utilized the chemical energy directly, then, the theoretically possible efficiency would be much nearer to 100 per cent than 30 per cent. The fact that it is only about 30 per cent would, then, be due to imperfections in the design of the mechanism, and would not be the result of any inherent physical necessity.

Let us now consider the magnitude of the quantities of energy involved in, for example, the activities of an ordinary man. First of all, let us take the case of an average-sized man resting in bed. Though he is doing no external work, his heart is beating, his blood is circulating, and his cells are all

keeping themselves in a state of good repair. Thus a substantial quantity of work is being done and in consequence, even in the resting state, oxygen is consumed, foodstuff is burned up, and heat is produced. In this condition of basal metabolism, as it is called, the heat production will be about 75 Kilocalories per hour or 1,800 per day. (If this heat could only be collected and used, it would provide us with a hot bath every morning!)

Let us now suppose that the man jumps out of bed and runs upstairs, thus raising himself by, let us say, twenty feet. The actual amount of mechanical energy required to raise his body through this height would be about one Kilocalorie. However, as we have seen, the efficiency of his muscles will not be more than 25 per cent, and owing to the somewhat crude and inefficient mechanism which the act of walking involves the efficiency as a whole will be less than this, so that his total extra energy production including heat will amount to perhaps 5 Kilocalories. If it takes 10 seconds to ascend the stairs the rate at which he is producing energy must be increased, for these few seconds, by 1,800 Kilocalories per hour, so that instead of being 75 Kilocalories it would be 1,875 Kilocalories per hour, which is twenty-five times the basal rate. If, on the other hand, he went for a walk over a level road, his rate of energy production would probably not exceed three times that of his resting state. Naturally, it would increase sharply whenever he came to a hill at all steep, for then, in addition to the relatively small quantity of energy required for moving his limbs backwards and forwards he would be doing work against gravity and so expending much more energy.

We know from experience that the moderately rapid ascent of a stair is a grade of exercise which, if continued long enough, represents quite hard work, though a man in good condition could go on for some considerable time without becoming exhausted. Experiments have shown that work can be continued for several hours if the intensity does not involve a

metabolic rate more than eight times the basal. When this figure is exceeded, the effort cannot be long sustained, and the worker soon becomes exhausted.

Let us suppose now that there was a dictator who had an unlimited supply of slaves, or human robots, at his disposal. Would it pay him to use them for the performance of mechanical work—as the Egyptians used human labour for the building of the pyramids? How many Kilocalories would he get from them for a penny? Let us make all the circumstances as favourable to him as possible. We will assume that the only expense he will have to meet will be the cost of their food, and that he provides them with a diet consisting only of the simplest and cheapest carbohydrate. Of course, they would not be able to go on living for long on such food. It would contain no proteins, no vitamins, nothing to repair the damages resulting inevitably from the wear and tear of existence. But an omnipotent dictator with an inexhaustible supply of robots would presumably not be worried by such trifles. He would just replace his men as they became ill. Let us assume that his men were super-Hercules, who could keep on working at a rate equivalent to the metabolism of 600 Kilocalories per hour for twelve hours each day; their total heat production would then be 7,200+1,800 Kilocalories =9,000 Kilocalories per day. It is probable that the carbohydrate would cost at least one penny per pound. If we remember that a gramme of starch produces 4·2 Kilocalories, so that one pound will produce barely 2,000 Kilocalories, we find that the food of each slave will cost at least fivepence per day. But he would be a very efficient worker indeed if he converted more than one-quarter of the 7,200 Kilocalories—the total extra metabolism—into mechanical energy. Thus, as far as work goes, the dictator would get only 1,800 Kilocalories for fivepence or 360 for one penny. Compare this with the figure of over 3,000 Kilocalories per penny provided by the steam engine!

It would be no advantage to feed his men on fat instead of

carbohydrate. Indeed, although fat provides 9 Kilocalories per gramme instead of about 4, the cost is more than proportionately greater. Protein would, of course, be much worse (see Fig. 24). It gives out just about as much heat per gramme in burning as does carbohydrate, and even the cheapest forms of it suitable for human consumption are much dearer. Clearly, although slavery was a paying proposition to the Egyptians in the absence of man-made engines, the thrifty modern dictator would free his subjects as much as possible from mere mechanical work and would seek to obtain his supplies of energy as far as he could from the powers of coal, oil, and water.

Now the human body needs not only fuel; like other engines it must have oxygen to burn the fuel. How much oxygen will be consumed by a man resting in bed and producing heat at the basic rate of 75 Kilocalories per hour or 1,800 per day? It happens that about one litre of oxygen is needed for every 5 Kilocalories of heat, regardless of the nature of the foodstuffs being burnt. It follows that he will remove from the air 360 litres of oxygen in 24 hours. This is about 12 cubic feet, and as air consists of about 20 per cent oxygen, it is equal to the oxygen contained in 60 cubic feet of air. A small room 12 ft. × 15 ft. × 9 ft. contains 1,620 cubic feet, so that it will take a resting man almost a month to use up all the oxygen in a room of this size. A person sleeping the night in such a room, even hermetically sealed, would evidently produce only a negligible effect on the oxygen concentration in the air, and so far from running any risk of asphyxia, he would find it quite impossible to detect any ill effects on this score.

But if the sleeper makes so little demand on the oxygen contained in the room, what about the carbon dioxide he produces? Does he run any risk of being poisoned, or otherwise disturbed, by its accumulation? The answer is at once obtained if we know that useful factor, the "respiratory quotient". This is simply the ratio of the volume of carbon dioxide produced to the volume of oxygen consumed. (In

virtue of Avogadro's Principle, the gas volumes are proportional to the number of molecules they contain, so that the respiratory quotient is the ratio of the number of molecules of carbon dioxide produced to the number of molecules of oxygen consumed.) We know that this is unity in the case of carbohydrates and about 0·7 in the case of fats; for proteins, it is intermediate in value. Our sleeper is likely to be burning up a mixture of carbohydrate and fat along with a little protein, so that his respiratory quotient might be about 0·9. We see at once that the volume of carbon dioxide produced will be even smaller than the volume of oxygen removed; in eight hours it would attain less than 0·3 per cent of the air present. This is not likely to disturb even the most delicate invalid.

Evidently it is not to ensure adequate supplies of oxygen or to get rid of carbon dioxide that we are advised to open our bedroom windows at night. In point of fact a bedroom is by no means hermetically sealed, even when the windows and doors are closed. The best-built house is far from airtight: few windows fit really tightly, and with doors and chimneys there is usually a very considerable replacement of the air going on constantly. Thus, even the small changes in composition calculated above will never be attained in practice. It is not denied that the open window habit is a good one—at least in a temperate climate like that of Britain—but its justification must be sought in considerations more subtle than the simple ones of oxygen consumption and carbon dioxide production.

CHAPTER IX

NATURE'S USE FOR OVERDRAFTS

THE animal body resembles the steam engine or the motor-car in that it can convert chemical energy into mechanical work; but it would be difficult to imagine a greater difference than that which exists between it and the engines which man has invented. The function is the same, but the structure is built on an entirely different plan and the detailed operations involved are in striking contrast. Even at a casual glance these differences are obvious enough. Animals are made of flesh and blood and bone; engines largely of steel, and other metals in minor degree. The wheel is the very essence of mechanical constructions which do work: nature seems to have avoided wheels altogether.

Man's engineering is based largely on the epoch-making discovery of circular movement and its special and peculiar virtues. To excel the greyhound in speed we build a device on wheels; even on the sea or in the air we propel ourselves with a special kind of wheel called a screw. The power and adaptability of wheel-engineering seem to be without limit: why, then, did Nature never give the principle a second glance? A first glance she gave it, for there exist small aquatic animals which move about by rotating rapidly; and others, still smaller, which crawl along by a queer process of turning themselves inside out continuously. But turning inside out would be fatal to the organization of multi-cellular animals, and even turning somersaults has become merely an amusement of the young.

It is easy to see that rotary motion would be of doubtful value to a land animal, for it is a trick which is only effective on reasonably smooth land surfaces, and no animal dare specialize its means of locomotion so far. The horse, which

adapted its means of locomotion to life in open prairies, paid for its loss of versatility by becoming practically extinct except in so far as man, for his own purposes, chooses to keep the species in existence.

But there is a much more cogent reason for nature's persistent neglect of the wheel as a mechanism. It is the difficulty of feeding it and letting it grow. A wheel, from the very nature of its function, must have no solid connexion with the rest of the structure; even in man's relatively simple machinery the task of lubricating or making electrical connexions with a rotating wheel has called for considerable ingenuity. In a machine which is not only self-lubricating but self-feeding, self-repairing, and self-reproducing, the wheel is outclassed entirely by nature's choice of the jointed lever. This principle of construction is capable of very elaborate application: probably no more accurate and versatile machine exists than the hand and arm of *Homo sapiens*.

The human machine is capable of a continuous output of work at the rate of about one-tenth horse-power,* a rate which is nearly the equal of a sewing-machine motor or a vacuum cleaner. A mountaineer climbing an easy slope at the usual pace of a thousand feet upwards per hour is exerting a little less than this. To meet emergencies we can, for perhaps half a minute, exert two to three horse-power, which is about the equivalent of the very lightest makes of motor-cycle, but to reach this limit the circumstances must be favourable. To rush upstairs as hard as you can, for example, is a bad choice of conditions for demonstrating your horse-power. The mode of movement is jerky and the gearing is all wrong. About one horse-power is as much as anyone can develop when running upstairs. Running to catch a train is a more favourable test: our gearing is more suited to it and our movements less jerky. The 100 yards' sprint can be done at an average speed of 21 miles an hour, and it has been calculated that something like 2 horse-power is exerted in achieving this. In skating the

* 1 H.P. is equivalent to work at the rate of 641 Kilocalories per hour.

movements are still more smooth, and a speed of 26 miles an hour is possible.

But if you really want to move quickly and efficiently under your own power the thing to do is to buy a bicycle—as every schoolboy knows. The maximum speed of an expert cyclist is in the neighbourhood of 36 miles an hour, and this in spite of the fact that the cyclist has to provide the energy to move the cycle as well as himself. The secret lies partly in the complete abolition of jerkiness and partly in the use of gears.

You or I could not lift a ton weight half an inch off the ground, yet either of us could lift 50 lb. through two feet, although this actually involves slightly more work. A navvy faced with the former job takes an appropriate set of pulleys and a rope and converts the impossible job into the possible one. He is using a gear, just as truly as the cyclist who "changes down" for a hill. For any given individual there is a particular speed of leg movement at which he can pedal most efficiently; for most people this is about thirty revolutions a minute, and the gears on the bicycle are chosen (or should be) so that when travelling at a comfortable speed on any reasonable gradient the legs make thirty revolutions to the minute. The lower gears thus enable the cyclist to maintain the same speed of leg movement whether going slowly up a gradient or more quickly down. Fig. 26 shows the results of an experiment undertaken to find out the most efficient speed of leg movement for one particular cyclist, riding one particular cycle; however the results are probably fairly typical.

Some living animals are only one-geared machines for locomotion; man has two gears, called walking and running; and the horse has four: the walk, the trot, the canter, and the gallop. Each of these is a true gear, for use over a given range of speeds, and it would be as wasteful of effort for a horse to gallop too slowly as to walk too fast.

Of man's two gears the lower is for use up to about 4 miles an hour (the exact figure depends on the individual), and the higher from 4 to 21 miles an hour. It is perfectly possible to

walk faster than 4 miles an hour or to run more slowly, but measurements of oxygen requirements show that neither achievement is worth while, since it costs more energy than to use the correct gear.

It is possible, of course, to use even the correct gear in a faulty fashion. In order to walk at 3 miles an hour you may choose a short, rapid pace or a long, slow one, or anything in

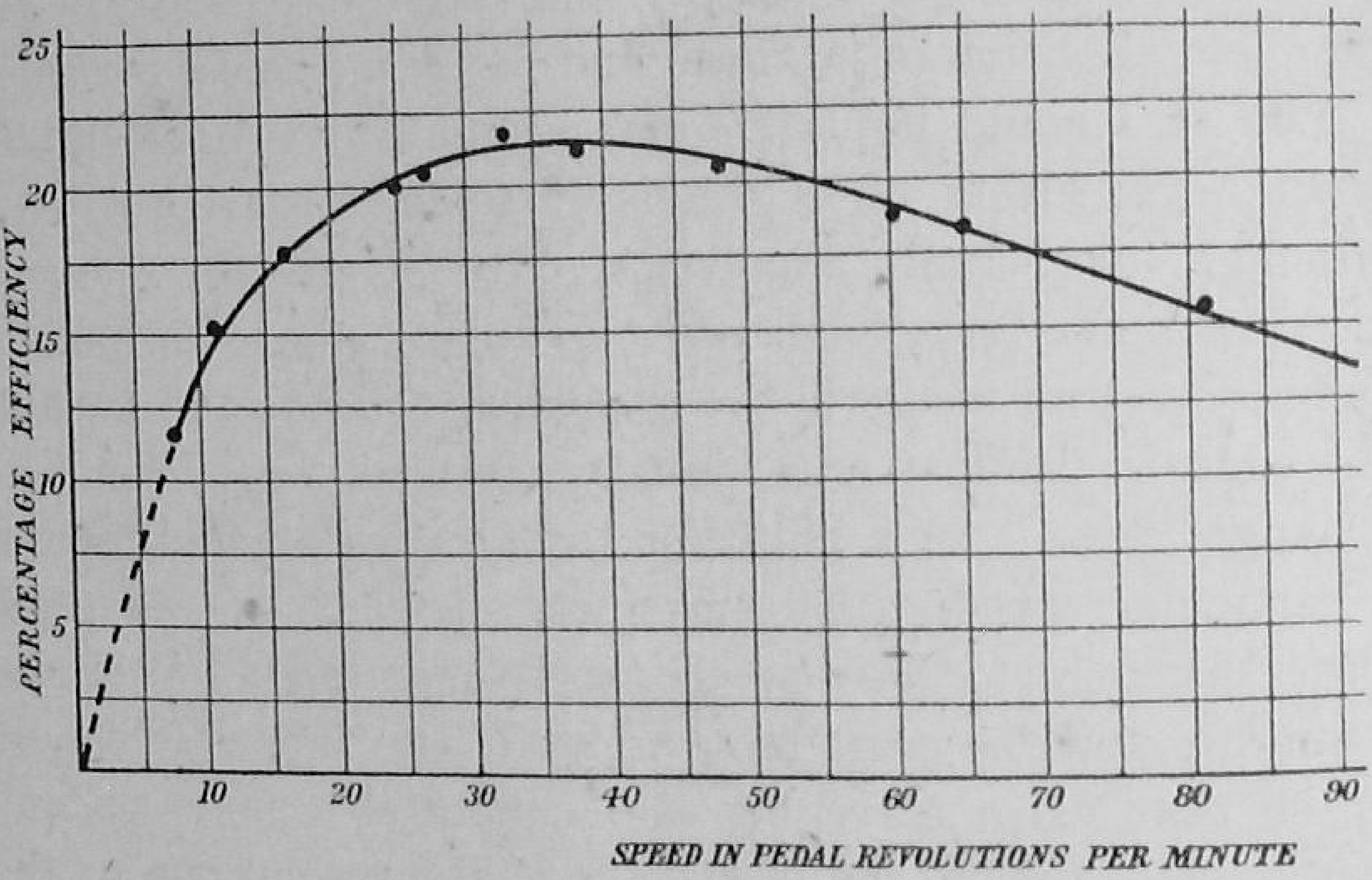


FIG. 26.—Showing the efficiency of a cyclist at different speeds of pedalling.
(Constructed from data obtained by Sylvia Dickenson, *Journal of Physiology*.)

between. But at either extreme efficiency will suffer: in one case because the rapid jerking of the limbs will waste energy, and in the other because the task of maintaining position and poise becomes unnecessarily fatiguing.

Nature, then, has achieved the principle of gearing without using wheels, though in a less elegant manner than is usually possible in man's metal-constructed wheel machinery. Nature's chief handicap lies in the difference of structural materials. For nature's machines have to be made of flesh and blood and bone, so that continuous rotation of any part about an axis is virtually impossible. But perhaps the most striking

difference between the two sorts of machine consists in the part played by water in them.

The presence of some water in its proper place is, of course, often essential to the working of various types of man-made engines and motors. The steam engine, for example, uses water as its working substance, but this is in a sense accidental, for, if water had been very scarce and benzene or chloroform very cheap and plentiful, there would have been no insuperable difficulties in producing engines using these fluids in the place of water. Indeed, it appears that in the case of turbines water is far from being the ideal working substance, and already attempts have been made to replace it, in whole or in part, by mercury, with the object of obtaining a more efficient conversion of heat into mechanical work. In the petrol engine, water is often used as a cooling fluid; here it is even more obvious that its use is accidental rather than essential. The ideal cooling fluid would certainly not freeze so easily on a winter's night, and even if it did it would not have the unusual property of expanding on solidification, and so bursting the radiator. But, since in most regions of the civilized world water is cheap and plentiful, whenever a liquid of some sort is required, water is employed if it will at all serve the purpose.

But the part which water plays in the animal body is a much more essential one. In the first place, we must remember that, apart from the bones, over 75 per cent of the body is simply water. The muscles, which from the mechanical point of view are the actual engines producing the energy to make us move, are pure water to the extent of over 80 per cent. The water is here an integral part of the mechanism. A motor-car or a steam engine without any water in it is still a motor-car or a steam engine: it takes only a few minutes to fill it up and at once it is ready to work. But remove the water completely from a muscle and it will turn into something quite unlike its former self—a hard, shrunken, mummified lump which no amount of resoaking in water will bring back to its former state.

The blood is, of course, also largely composed of water, but here the function of the water is perhaps more like that which it has in the motor-car. It plays the part of a carrier, carrying not only heat—as in the car engine—but fuel and oxygen to the tissues of the body. It is just conceivable that in another environment nature might have employed some other fluid in its place. But, however this may be, in the case of all the really living tissues of the body the water which is present is an integral part of the living structure, and any scheme for dispensing with it altogether or for replacing it by some other liquid, such as alcohol or liquid ammonia, would require a fundamental alteration of all the vital processes involved. It would not be a question of merely minor changes in design, such as might be needed in building a locomotive to work with chloroform in the boiler, for the delicate structure of the muscle proteins would disintegrate when removed from the aqueous solution in which they are normally bathed; and besides, the whole system of delicate and interdependent chemical reactions involves the co-operation of water at almost every point.

What, then, is the nature of this extraordinary mechanism —a living muscle—and how does it work? This is one of the key questions in physiology and biochemistry. Although the answer to it is as yet far from complete, some progress has been made in unravelling the very complicated problem which a living muscle presents.

The general appearance of muscle is familiar enough to us all. The steak we had for lunch was typical. In cooked form it was brown and (we hope) relatively easily disintegrated into small fragments; originally it was red and juicy and more tough and elastic. The change depends on the fact that, apart from water, the chief constituent of muscle is protein, and the effect of heat on muscle protein is to denature it—to convert it into a less soluble and more flocculent form (see p. 83).

But muscle does not consist merely of water and protein. To enumerate all the known components of a lump of beef

would be quite a long business, fortunately not needed for our purposes. The muscle contains components which are fatty in character; this fat serves in part as fuel to supply the energy needed for the production of mechanical work, but it also helps to build up the very elaborate architecture of the cells of which the muscle is composed. In addition to fat, a muscle contains carbohydrate in the form of glycogen, to which we have already referred in Chapter VI. This is perhaps the most important source of muscular energy, at least for the ordinary activities of life. Our bodies are like furnaces which can burn either wood or coal. Wood, which is chiefly carbohydrate, is more easily kindled and burns faster; but the coal, to which we may compare fat, produces more energy in proportion to its weight and is especially useful for prolonged heavy labour.

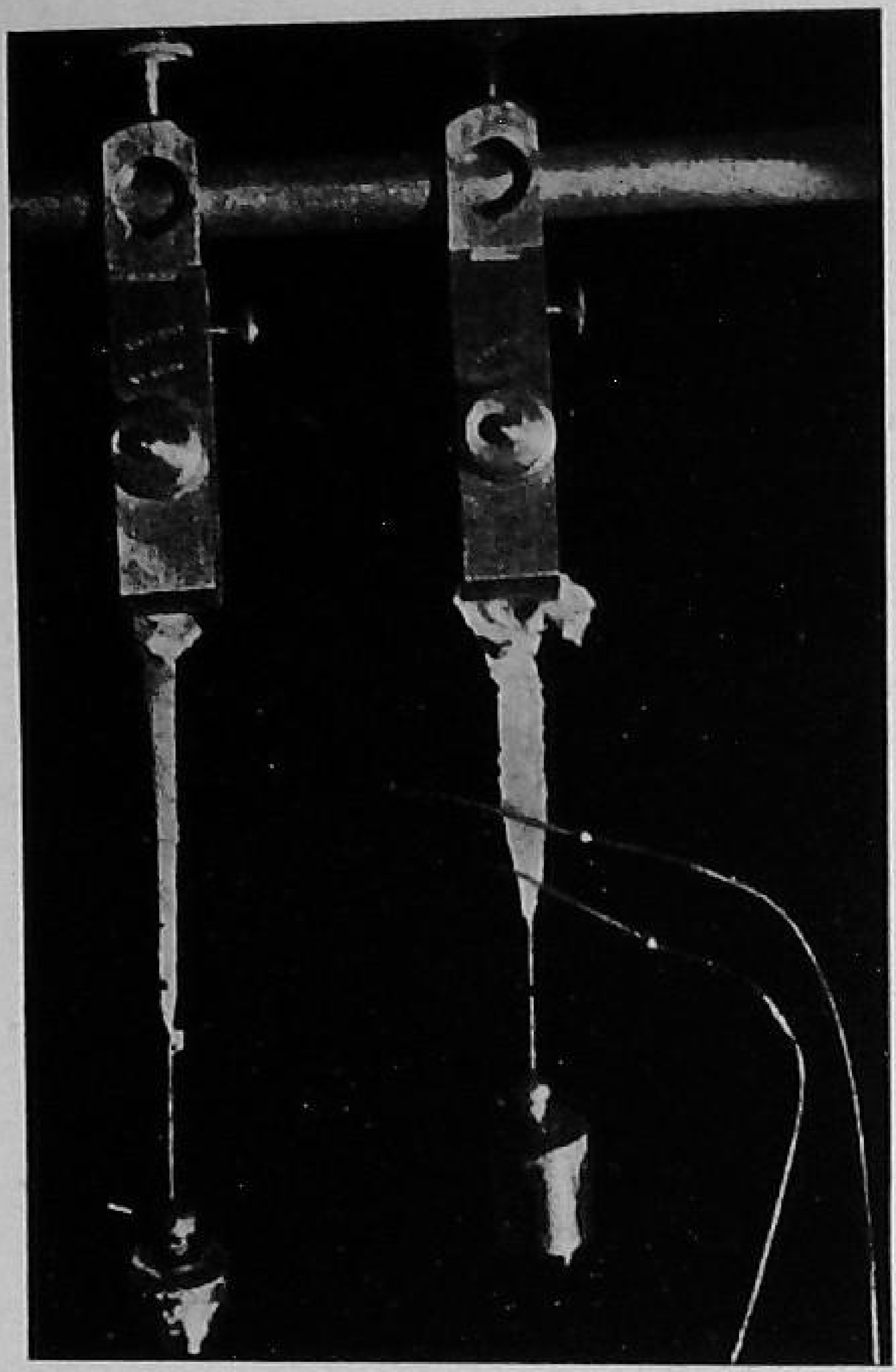
These substances, proteins with a little fat and carbohydrate, contribute to the structure of the muscle, but many other substances are there besides, smaller molecules dissolved in the water of which the muscle is so largely composed. We have salts—sodium chloride, potassium phosphate, and others in smaller amounts. These seem necessary to provide the proper environment for the muscle protein and other colloidal constituents of the cell. Then there are in small traces the substances which together constitute the immediate food supply of the tissue, and which are constantly diffusing from the blood in the capillaries into the substance of the muscle. These include sugar and amino-acids. Similarly, the final products of muscular activity are found on their way out to the blood-stream. The chief substances in this category are ammonia, left over from the burning of amino-acids; carbon dioxide and water, which result from the burning of any organic compound; and lactic acid, which comes from sugar molecules broken down in the course of muscular work.

This lactic acid, as we shall see later, is a very characteristic product of the active muscle, and it has been one of the great problems of biochemistry to find out just what its appearance means in the mechanism of muscular contraction.

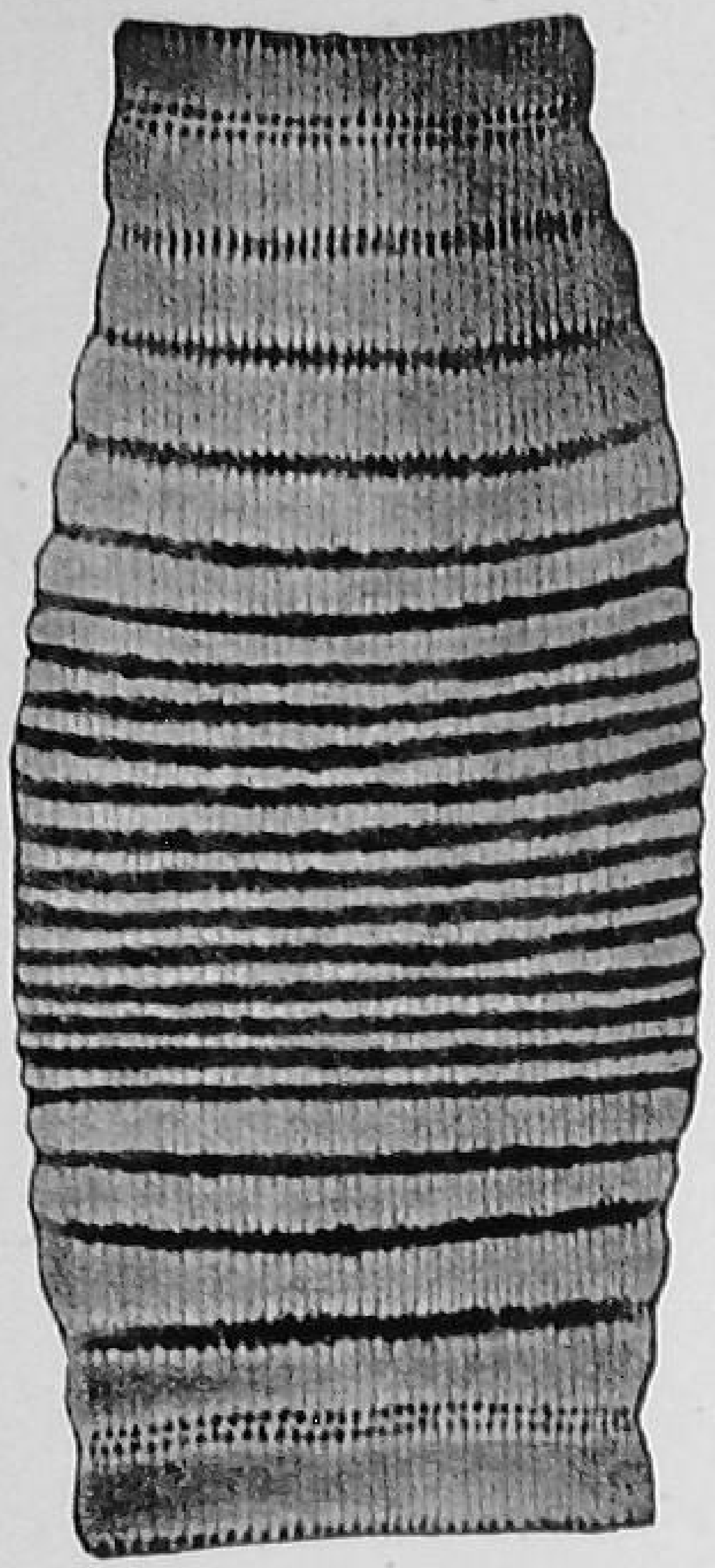
Lastly, there is found in muscles a set of substances which form links in the chain of chemical reactions making muscular contraction possible. For the utilization of a foodstuff as a source of energy for mechanical work is not a simple one-stage process. It can only be done efficiently by means of a complex chemical mechanism, strictly controlled at every point and involving many reactions carefully co-ordinated with each other. The last twenty years have seen a great increase in our knowledge of this system, though it cannot be claimed that we have done more than scratch the surface of this fascinating field of research. Nevertheless, there is now a broad agreement as to the course followed by one at least of these chains of reactions. Finality is still far off, but the skeleton scheme put forward by the two great German biochemists Otto Meyerhof and the late Gustav Embden gives us a working picture of the steps involved in the utilization of carbohydrate fuel. The four or five intermediate compounds postulated by these authors have been isolated from muscle, the reactions postulated are all inherently reasonable, and most of them have been demonstrated outside the body.

The particular chemical system concerned with the utilization of glycogen is but one of several present in the muscle, and about most of the others we do not yet know very much. We have been able to trace in nature's machine one train of cog-wheels, but it is evidently only part of a more complicated set. Here and there we catch a glimpse of other wheels: some of these seem connected with our original series; others appear to be isolated and apparently useless, yet we can be sure they are not there for nothing. Unfortunately the machine is so delicate that it cannot be taken to pieces without breaking up many of its component parts, but by a careful study of what pieces we can collect, by poking into the machine while it is running and finding out how a particular disturbance interferes with its working, it is hoped eventually to discover the complete plan.

The actual muscle, then, is a complicated protein structure equipped with stores of fat and carbohydrate as fuel, and



The two sartorius muscles of a frog, each loaded with a twenty gram weight. The muscle on the right has shortened under the electrical stimulus applied through the electrodes. (See page 147).



A photo-micrograph of a single muscle fibre contracting. (See p. 147).

(By permission from Schafer's Essentials of Histology.)

Two photographs of the heart of a frog removed from the animal and mounted so as to maintain an artificial circulation of salt water. Left: contracted. Right: relaxed. The fluid flows back into the relaxed heart under gravity from the reservoir.

(Photographs by Dr. W. Tebrich.)

steeped in water containing a diverse assortment of substances in solution which either are necessary for the proper functioning of the tissue or represent the products of its metabolism. Though the details of the structure are far too fine to be seen under the most powerful microscope, the gross structure of the muscle is easily demonstrated. It consists of long, fibrous cells, and the characteristic contraction of the muscle as a whole depends upon the simultaneous and co-ordinated contraction of these separate cells (see Plate II). This happens when the nerve attached to the muscle is stimulated. The movement of our bodies as a whole depends on the co-ordinated action of numerous muscles all under the control of the central nervous system. The whole constitutes a machine of astonishing delicacy and complexity.

Not only does the muscle differ in its type of structure from a man-made machine, but there is also a marked contrast between them in their modes of working. Inasmuch as we obtain our energy by burning food and this is done in our muscles, these must be regarded as internal combustion engines, just like the engine of a motor-car; but there is at least one respect in which our muscles have a very remarkable advantage over the petrol engine. The latter is strictly dependent for its power from moment to moment on its oxygen supply. Indeed, we use this fact to control it, for the accelerator pedal of a car regulates primarily the rate at which air is admitted to the engine. But it is a characteristic of nature's engines that, though just as dependent on oxygen in the long run, they are not so dependent from moment to moment. Though every movement must be paid for by the absorption and use of the proper amount of oxygen, *the payment need not be made at once*. It is as though we kept inside our bodies a secret store of oxygen on which we could draw in emergency, replenishing the store afterwards; and, indeed, this was thought for a long time to be the actual explanation, but the idea had to be given up, for nobody could find the hidden store. The real explanation proved to be very different.

We have seen that a litre of oxygen can release about five Kilocalories of energy, and of this about a fifth can appear as work, so that whenever we do work, we require about a litre of extra oxygen for every Kilocalorie of work we do. When the work is very light, we consume this extra amount of oxygen practically at the same time as we do the work. We pay for the work as it were with ready money; once the work has been done, the transaction is finished and we are ready to do more. But suppose we want to perform some much harder labour. To pay for this on a ready-money basis would involve an immense speeding up of all the oxidation processes which are involved in the complete mechanism of muscular contraction, including the transport of oxygen from lungs to muscles and of carbon dioxide in the opposite direction. Now some of these processes can be accelerated easily enough, but others, notably the physical ones of transportation and diffusion, are much more sluggish. Even a rich man may find it inconvenient or impossible to realize his securities at a moment's notice. He falls back on an overdraft. And so nature has very conveniently set at the disposal of the animal organism an arrangement whereby it can obtain an overdraft in respect of its oxygen supply. By means of this ingenious mechanism, the work done does not need to be paid for at once in terms of oxygen consumption. For the time being what has been called an "oxygen debt" is created. This has, of course, to be paid off by the consumption of extra oxygen after the work is over; indeed, like a banker who is taking no risks, nature limits this overdraft to about twelve litres of oxygen, and insists on the repayment being made promptly. The energy value of twelve litres of oxygen is not very much, but it would see you out of a crisis lasting up to half a minute or so.

A man who has just rushed up a long flight of stairs finds himself quite out of breath; he puffs and pants for perhaps several minutes before he recovers, and if he cannot rest, if he is forced to go on, he must of necessity slow down. He finds

it quite impossible to keep up his original fierce speed. If he is trying to arrive on time for an appointment he may suffer the embarrassment of arriving flustered, panting, and speechless, but without the aid of the "oxygen debt" mechanism in his body he could not have hurried and would certainly have arrived late, for on current oxygen supplies most of us cannot manage more than a fast walking pace or a steady trot.

The practical importance of this power of the organism to contract an oxygen debt can scarcely be exaggerated. The general effect is to enable the animal body to perform short spells of work at a much more intense rate than would otherwise be possible. The mouse escaping from the cat, the tiger springing upon his victim, the horse galloping madly down the racecourse, the boxer fighting desperately to knock out his opponent—all these are entering into oxygen debt, to be paid back as soon as the emergency is over and there is time for rest and recovery.

In certain forms of sport and athletics the importance of oxygen formation is particularly great. For the purposes of his Presidential Address to the British Association, Section I, in 1925, Professor A. V. Hill collected together a series of world records in running, walking, and skating over distances ranging from 100 yards to 100 miles. He assembled these on a diagram, plotting the average speed of each race against the distance involved; the figures for each mode of progression gave a series of points lying on a smooth curve, and these curves enable the eye to take in the broad facts almost at a glance. Certain of the points on his diagram (reproduced in Fig. 27) are now superseded by new world records, but the alteration necessitated in most of these cases is so small as to be barely discernible on the graph.

Consider the curve labelled "men running". The fall in average speed as we pass from shorter to longer races only reflects common experience: the interesting point is the suddenness of the fall in the region of the ¼-mile race. For races of quite short duration, such as the 100 or 200 yards,

the athlete's speed depends only on the maximum speed at which he can move his legs—the question of oxygen supply hardly enters, for he can work almost entirely on an oxygen overdraft, paying this off when the race is finished. For long races, on the other hand, races of 1 to 10 miles, the ability to incur an oxygen debt is of no value, except in the finishing

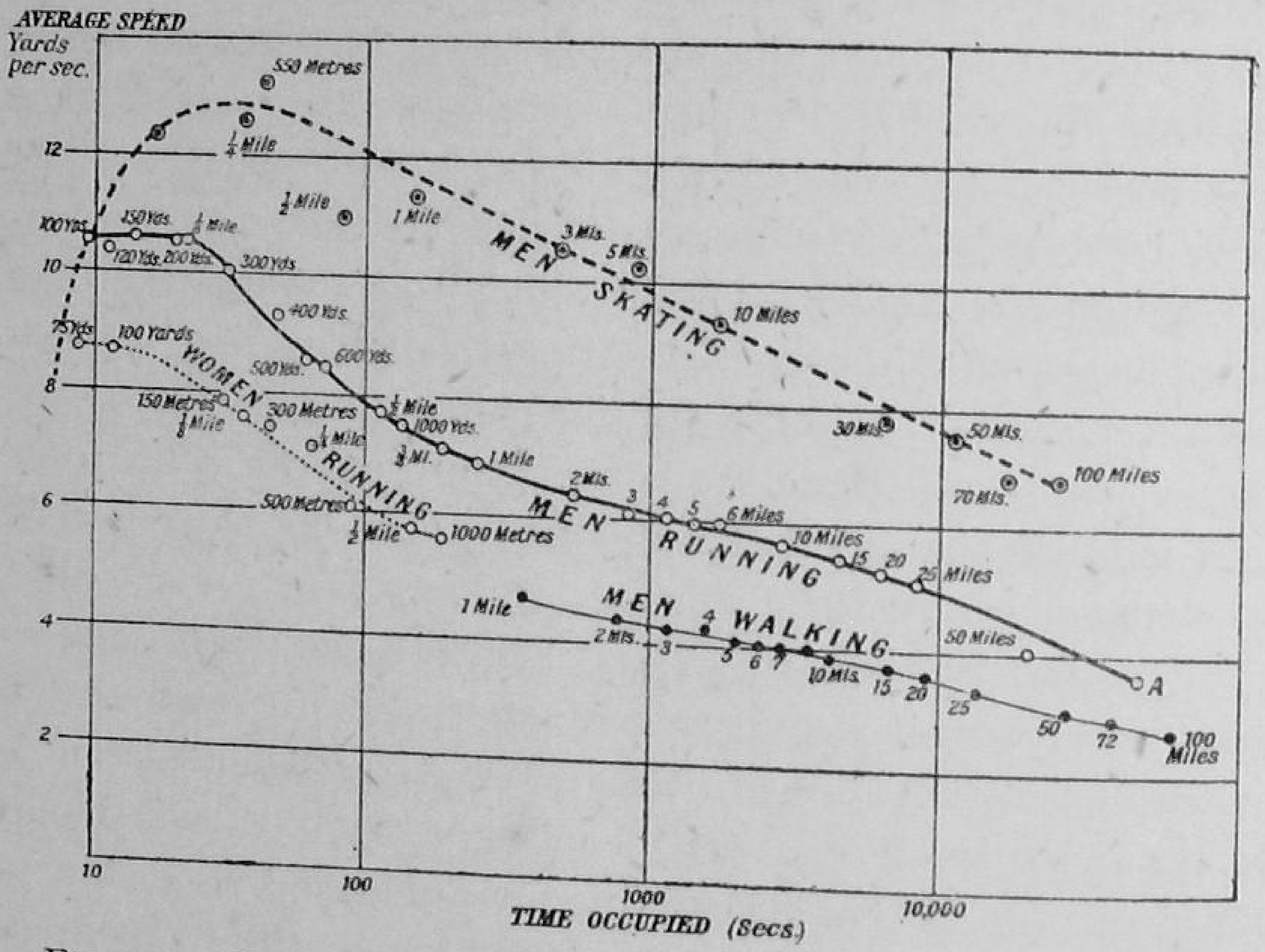


FIG. 27.—The best average speed for races of different durations. (After A. V. Hill, *British Association Reports*, 1925.)

sprint. Most of the race must be run on current oxygen supply, and the runner's speed is limited by his ability to absorb oxygen rapidly. Now this faculty is quite different from the ability to move the legs fast, and for this reason it is unusual to find an athlete reaching championship form in both classes of racing. It is in the ¼-mile that the ability of a runner to contract a large oxygen debt is of decisive importance; this race is too long to be treated as a sprint, but not long enough to be run as a long-distance race. It will, in general, be won by the man who can get the biggest overdraft and so come most nearly to treating the race as a sprint.

And now, we must inquire, what is the inner mechanism which makes it possible for the organism to contract an oxygen debt? What is it which limits the amount of the debt which can be contracted? The situation is rather similar to the case of a motor-car of which the engine is used only to charge, and keep charged, an electrical storage battery which in turn drives an electric motor coupled to the back wheels.

As this car cruises along the level, the petrol engine will in general supply electricity to the battery as fast as the electric motor is taking it out. The accumulator, indeed, might just as well not be there. If a short but steep hill has to be climbed, the motor will need electricity at a much greater rate than the engine can supply, but that does not matter, for the storage battery can stand the drain if it does not go on too long. And when the hill is surmounted the engine can work a little harder than usual, for the next half-hour or so, until the battery is again fully charged. The whole point of this arrangement is that the battery protects the petrol engine from sudden large demands for energy, and in consequence a motor-car of this design could achieve, for short spells, a performance far above that of a car of conventional design equipped with an engine of the same horse-power. There is no sense in building cars of this sort: it happens to be more economical to build bigger petrol engines. But there is plenty of sense in having our bodies built on this principle, because our difficulty is that of taking in oxygen quickly enough. To sprint upstairs on current oxygen supplies we should need hearts, lungs, and arteries of impossible dimensions.

Now it is to be observed that what really happens in a storage battery is that the lead, or whatever may be within, undergoes a chemical reaction during the process of discharge, while the electric motor is going, and that the process of recovery, or recharging, involves the reversal of this reaction, bringing the contents of the accumulator back to their original state. What, we may ask, corresponds in the muscle to the chemicals inside the accumulator?

We have to look for a chemical reaction occurring in muscles during activity in the absence of oxygen, and, *ex hypothesi*, it cannot be an oxidation. Now the chemist knows of no method of getting energy from fats, nor, generally speaking, from proteins, save by burning them; and all the evidence so far goes to show that nature has found no way either. But with sugar (or glycogen, which is just condensed sugar) there is such a method. It is to break each molecule of sugar ($C_6H_{12}O_6$) into two molecules of (neutralized) lactic acid ($C_3H_6O_3$). About a tenth of the energy is obtained that could be released by burning the sugar. This is not as wasteful as it looks; indeed, it is not wasteful at all, for the lactic acid can be burned later when there is plenty of oxygen available.

Now experimental work shows that when a single muscle, removed from an animal but still living and able to contract, is made to do work in the absence of oxygen, the glycogen in it disappears and lactic acid is produced. The obvious inference is that in this chemical reaction, the conversion of glucose into lactic acid, we have the mechanism which corresponds to the lead and sulphuric acid within the accumulator, and that it is through this reaction that the oxygen debt is contracted. When the muscle is supplied with oxygen after its spell of work the lactic acid disappears again. Some of it is burnt to provide energy, and with the aid of this energy the rest is stored once more as glycogen. The accumulator is recharged by the internal combustion engine.

The extent to which we can avail ourselves of this device for increasing our top speed depends on the amount of lactic acid we can tolerate in our bodies, for any kind of acid is unpleasant to have about. The limit seems to be about three ounces and it is reached in less than a minute when we are going "all out". The production of even this small amount of acid means that about twenty-five Kilocalories of energy can be released in under a minute *without using oxygen*.

The extra "pace" made possible by the glycolysis mechanism seems not to suffice, however, and in the fresh muscles of

animals we find stores of a chemical compound which act as a reserve of even more rapidly mobilizable energy. This compound (called phosphocreatine) is found in all muscles, but it is only in muscles such as those of the limbs which must on occasion move very fast indeed that we find considerable stores of it maintained. When this substance breaks up, as it can very easily without the use of oxygen, it gives off energy which is used by the muscle. The amount of "latent" energy stored in this way in your muscles is about five Kilocalories—

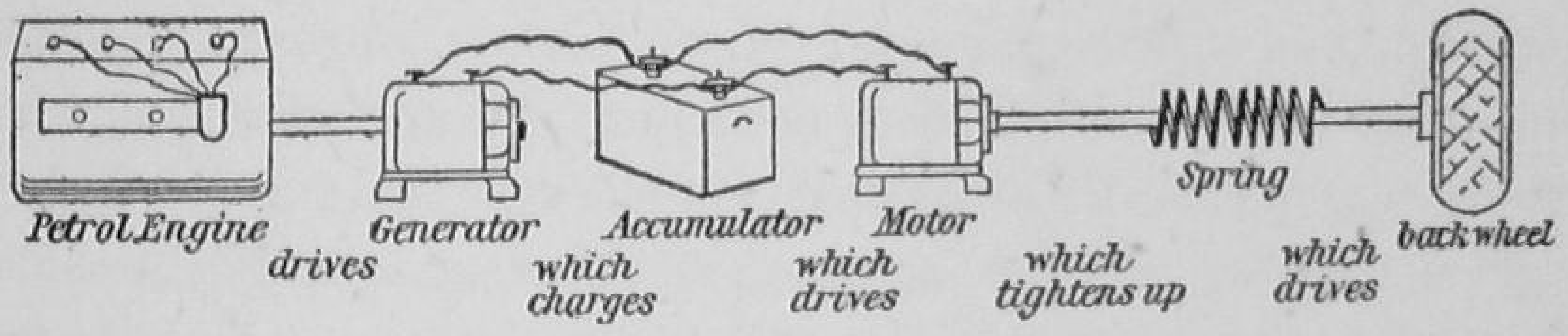


FIG. 28.

not very much, but enough to get you away rapidly from a mad bull if the field is not a very large one. The function of this highly "labile" source of energy can be illustrated if we go back for a moment to our biological motor-car and uncouple the electric motor from its back wheels. Let us incorporate a large and powerful clock spring, so that the electric motor now serves merely to wind up the spring, which latter, when released, can impart to the car a catapult-like acceleration. The spring therefore serves to give the car a flying start, after which the electric motor takes up the load and re-coils the spring in the first few minutes, then the petrol engine gets going, recharges the storage battery which has been partly discharged, and settles down to keep it fully charged. And there you have the up-to-date model of the biological motor-car.

The machinery we use in our muscles is not peculiar to human beings. Not only is the same mechanism common to all mammals, birds, reptiles, and fishes—at least to all that have been examined—but something very similar indeed is used by the invertebrates, the lobsters, spiders, insects. It has been shown that even the single-celled animal *Amoeba*

proteus has some chemical trick at its disposal to enable it to survive a temporary shortage of oxygen, apparently by contracting an oxygen debt. And more remarkable still, the yeast organism, which is a plant, not an animal, has a chemical mechanism very similar to our own on which it relies when oxygen is deficient. The yeast cell does not move and has no muscles, but it needs a constant supply of energy to keep alive, just like all other living things. To get this energy when no oxygen is forthcoming it converts sugar into alcohol, a process which yields about as much energy as the other trick of turning it into lactic acid. Neither procedure is a simple one-stage affair; several steps are involved; and the similarity of the two mechanisms is shown by the fact that all steps but the last one or two are substantially the same in both. (The yeast cell does not have to allow for sudden emergencies requiring severe exertion, and probably for this reason it has not the additional "phosphocreatine mechanism" possessed by all but the simplest animals.)

Since the same amount of energy can be tapped in either case, why do we produce lactic acid in our muscles and not alcohol? It is no answer to say that alcohol is an intoxicant, even a poison. It is only poisonous to us because we have not developed the knack of burning it rapidly. The ability could have been acquired, and indeed to all appearances *is* acquired by some enthusiasts. Moreover, the alcohol, being volatile, could be eliminated in the breath, just as we normally get rid of the volatile carbon dioxide which is formed in our bodies; but there, probably, is the answer to the question. Such elimination would waste considerable amounts of energy, for what is eliminated is lost and cannot be subsequently burned as fuel.

Why, then, does the yeast plant produce alcohol, and not lactic acid? One would like to think that this pleasant habit arose from a desire on the part of the yeast organism to cheer mankind and add to the gaiety of nations. But the truth is more chemical and less romantic. Evidently a yeast cell

growing in the absence of oxygen prefers to waste energy in the form of the volatilizable alcohol, rather than of lactic acid, which would produce an uncomfortable acidity in its neighbourhood. It is all a matter of taste.

There are, indeed, certain micro-organisms which produce lactic acid from sugar, and to this extent more closely resemble our muscles. These are the bacteria which bring about the souring of milk, to the annoyance of the housewife every summer. It has not been proved that they use the same method as our muscles—investigation of the biochemistry of micro-organisms is exceedingly difficult—but what evidence there is goes to show that the route used is essentially the same.

And so, starting with athletics and exercise, we find ourselves talking of beer and sour milk. The transition is a very natural one, for it depends on the real affinity of the processes involved in these apparently so different activities. All are concerned with the breakdown of the sugar molecule. At an early stage in organic evolution, nature seems to have found out a way of doing this which suited her. Subsequently she has applied this one method, with minor modifications, over and over again. This economy in original ideas, this exploitation to its limits of a good discovery and its application in many diverse ways, these are very characteristic features of nature's factories. One touch of nature makes the whole world kin.

CHAPTER X

AN UNSOLVED PROBLEM

UNTIL very recently in his history, man drew only sparingly on inorganic nature to supply him with energy. He used the windmill and the sail for trapping the energy of the wind, and he had water-wheels which gave the power required to grind his corn or work his looms. But these sources of energy did not add very much to his main supply from horses and oxen and, above all, from the efforts of his fellow-men and often women. Until the middle of the eighteenth century, the supply of energy from non-living sources was not only very small as compared with our present vast flow; there is also an important qualitative difference. By far the greatest amount of the energy we now use comes from the combustion of coal or oil. It comes to us as chemical energy and we are clever enough to be able to convert it for our uses into mechanical energy. The energy of the winds and of the streams needs no such conversion, for it is there in the first place as mechanical energy, and so it was relatively easy for man to harness it to his needs. The modern industrial age began when the problem of converting chemical to mechanical energy was solved.

Perhaps a thousand million years previously the same problem had already been solved on this planet. In the course of evolution, animals had developed muscles. The essential purpose of a muscle is to do mechanical work at the expense of the chemical energy which is liberated in the course of the metabolic processes going on within it. In plants the situation is rather different. They are able to trap the energy of sunlight and store it as chemical energy, but are unable to convert either radiant energy or chemical energy into mechanical work; it is only the animal organism that has solved this difficult

problem. The contractile muscle is Nature's answer; how does this remarkable contrivance work?

Let us first look at man's ways of solving the problem. He has, in fact, worked out two quite distinct solutions. One of these is represented by a steam engine; the other by an electric motor driven from a battery.

In the steam engine, the chemical energy is not directly converted into mechanical energy, but it is first converted into heat at a high temperature. This high temperature heat in the water and steam within the boiler is partly allowed to escape at a considerably lower temperature in the exhaust water, but some of it is trapped and converted to mechanical energy by the mechanism of the engine. In the battery-motor system, there is also an intermediate stage; the chemical energy of the battery is converted into the energy of the electric current, and this energy is then transformed into mechanical energy by the motor. But there is no stage at which the energy is present in the form of heat.

As we have seen (Chapter VIII), heat energy consists in the disorganized motion of the molecules, and at best is only partially available for conversion into the organized motion we call mechanical energy, by means of which we can do work. The very fact of converting the energy into heat means that it is no longer possible to convert it all into work. A heat engine, by its very nature, can have only a relatively low efficiency; and this, of course, applies to an internal combustion engine or a jet turbine, as well as to a steam engine, for in any of them the energy first becomes converted into heat.

The second type of system for converting chemical energy into work does not suffer from this inherent disadvantage; in our combination of battery and electric motor there is no stage at which the chemical energy is developed as heat, and there is no need for any temperature difference such as is an essential feature of the heat engine. There is no doubt that if we were interested to do so, and had the money to spend on the project, we could build an apparatus which would produce mechanical

are involved, what chemical and physical changes take place when a muscle contracts.

The muscle does something which is quite outside man's power at the present time—it can burn fat and carbohydrate and convert part of the liberated energy directly into mechanical work; that is to say, without this part of the energy appearing at any stage as the disorganized energy of molecular motion.

The chemical and physical system present in muscle which effects this transformation of chemical energy into mechanical work is baffling in its complexity; all the more so as it is very different from any engine so far built by man. We know a great number of separate facts about the constituents present in muscle, and how they behave separately and in combination, but there are big gaps in our knowledge, and the essential problem of the precise method by which chemical energy is converted into mechanical work still eludes solution. Some of the facts which appear significant we have already become acquainted with in the last three chapters. Let us try to bring them into relation with each other.

On the one hand we have the actual contractile substance present as minute fibrils within the muscle fibres; this is composed of the protein myosin, or rather, according to Szent-Györgyi, of an association of two proteins, myosin and actin. Myosin, and more especially the actin-myosin complex, exhibit remarkable physical properties; their solubility and the viscosity of their solutions are very sensitive to relatively low concentrations of salts. This great dependence of the physical state on the environment is surely a cardinal property of these muscle proteins.

Apart from myosin and actin, the muscle contains numerous other proteins, and many of these are enzymes which promote particular reactions. We have already referred to some of them. There is the set which promote and control the conversion of glycogen into lactic acid; this is achieved in a series of steps each of which has its appropriate enzyme. From the

point of view of muscle contraction, the important fact here seems to be that phosphate is taken up and charged with energy; the energy is that liberated by the glycogen turning into lactic acid (p. 152). Such energy-rich phosphate is present in a compound known familiarly as A.T.P., a contraction for its proper name, adenosine triphosphate. Now, as far as is known at present, the chemical action which is most closely associated with the actual physical contraction of muscle is the splitting up of A.T.P., with the liberation not only of inorganic phosphate, but of a considerable quantity of energy besides. This strongly suggests that it is this energy-rich phosphate in A.T.P. which is the source of the mechanical energy liberated in muscle contraction. The only purpose of the complicated chemical reactions involved in the splitting of glycogen into lactic acid would on this view be the production of A.T.P.

The muscle tissue not only converts glycogen into lactic acid; it also oxidizes fats and carbohydrates, and these processes of oxidation supply much more energy than the fission of glycogen into lactic acid; one gramme of glycogen burned produces in fact about seven times as much energy as the same amount of glycogen broken up into lactic acid. Our knowledge of these oxidation processes is still very rudimentary—various separate reactions have been discovered, and certain series of reactions have been established—and yet it is certain that practically all the energy of muscular contraction in the intact animal comes ultimately from these oxidations. What is the relation of these oxidations to the breakdown of glycogen into lactic acid? It may be either direct or indirect. It is possible, indeed very probable, that A.T.P. is in fact formed by certain of these oxidative mechanisms. This would suggest that the splitting of glycogen and the oxidation of fats and carbohydrates are two independent processes both of which furnish A.T.P., from which the muscle obtains a supply of energy for its contraction. But it is also possible that the oxidation processes may be associated with the conversion of lactic acid

back into glycogen; this is a reaction which requires energy and the associated oxidation would provide it. Indeed, we know that after severe exercise the body contains a good deal of lactic acid, formed while the "oxygen debt" was being incurred, and the repayment of the debt is simply the result of the increased oxidation required to provide the energy needed for the reconversion of the lactic acid into glycogen. It seems possible that during even mild exercise a good deal of the energy comes in the first place from the glycogen-lactic acid breakdown, and that the oxidative processes are mainly used to rebuild the glycogen from the lactic acid.

If we are confronted by a mass of facts, baffling in their number and complexity, it is imperative to search for the essential points and to concentrate our attention on them. Even if we are not quite certain what the essential points may be, it may greatly help our handling of the data, provisionally to make a guess as to where the essence of the situation lies, in the hope that the unessential may fall readily into place and a comprehensible picture be obtained of the whole. This is indeed the secret of all scientific theorizing; to pick out the essential and dominant factors in a situation, to explore their effects, and then, if necessary, to allow for minor factors in the form of secondary disturbances or perturbations.

In our present problem of the mechanism of muscular action, then, we make the guess that the essential result of all the complicated chemical processes is to provide a supply of "high-energy" phosphate in the form of A.T.P. This energy may come from the splitting of glycogen into lactic acid, or it may come directly from oxidative processes. The important point is that it is locked up in the A.T.P. molecule ready to be utilized by the contracting myosin of the muscle. This picture may be an over-simplification, but it does seem to be in conformity with the large number of known facts.

The crux of the problem, then, is, how is the chemical energy tied up in the A.T.P. actually converted into the mechanical energy of contraction? We just do not know. But there are

one or two observations which suggest that we are on the right route to the solution of this problem. In particular, there are certain relations between A.T.P. and myosin which are very remarkable in themselves and appear to be highly significant for the present problem.

If myosin is the contractile constituent of muscle, then muscular contraction implies some change in the physical state of the myosin. Now A.T.P. does seem to exert a very definite and curious effect on myosin molecules. This is shown on dissolved myosin molecules and much more spectacularly by certain experiments described by Szent-Györgyi. This famous biochemist with his pupils prepared filaments of actomyosin by squeezing a concentrated solution of actin and myosin through a small hole into water containing traces of suitable salts. The actomyosin was precipitated as a long, fine filament. A trace of A.T.P. was then added to the water in which this filament was suspended. The result was a remarkable contraction of the fibre to a fraction of its original size.

If A.T.P. exercises a peculiar action on myosin and the complex of myosin and actin, so also conversely, myosin has a very special effect on A.T.P. This effect was first detected by the Russian biochemists Engelhardt and Lyubimova, and their results have been confirmed by other investigators. Purified preparations of myosin function as an enzyme which removes a single "high-energy" phosphoric group from A.T.P.; this is precisely the chemical reaction which we believe is the immediate source of the energy required for muscular contraction.

It may perhaps be an over-simplification to say that myosin is the enzyme which splits off the phosphate group from A.T.P. The observed fact is that fresh preparations of myosin possess enzymatic activity. But Engelhardt and Lyubimova themselves observed that the activity of myosin was of a lower order than that possessed by other pure crystalline enzymes; and recently the American workers, Dr. and Mrs. Cori, have separated what seems to be the enzyme itself in a much more

active form. The association of myosin with the enzyme is evidently a very intimate one, and from the point of view of the mechanism of muscle contraction it would not seem to matter very much whether the enzymatic power resided in chemical groupings directly attached to the myosin molecule or were located on another protein molecule in intimate contact with the myosin. We encounter bonds of all degrees of strength, from very weak ones such as cause the molecules of liquids to cohere, to very strong ones, as between the carbon atoms in a diamond. The myosin-enzyme complex may well be held together by bonds of an intermediate strength, stable under the conditions of recrystallization as they normally exist, but easily broken when special trouble is taken to break them.

We are presented, then, with a most intriguing situation: one which fixes our attention and excites our curiosity. On the one hand we have an enzyme very closely associated with myosin, which controls the liberation of chemical energy from the "high-energy" phosphate in A.T.P. On the other hand, we have the myosin-actin complex, highly sensitive in its physical state to the presence of A.T.P., which causes it to shrink as it presumably shrinks in the contraction of the muscle fibre. How can these facts be incorporated in a model of the contractile tissue? We cannot at present give a confident answer to this question, and perhaps it is futile to hazard a guess where so much is uncertain and unknown. But it is difficult to resist the temptation to try to design on paper a molecular mechanism which would behave in the right sort of way and suggest at least the general nature of the molecular processes involved in the act of transforming the chemical into mechanical energy.

Let us imagine, then, a structure composed alternately of springs (S) and extensible "lazy-tongs" (T), as shown in Fig. 29. In this model, the "lazy-tongs" represent the myosin-actin-enzyme complex, and the springs an elastic constituent of the muscle fibril; of course, muscle like many other tissues has elastic properties which it is convenient to represent by these

springs. Notice that when the tongs shorten, either the whole model shortens (if the ends X and Y are free), or if both ends are fixed the springs are stretched and a tension is developed.

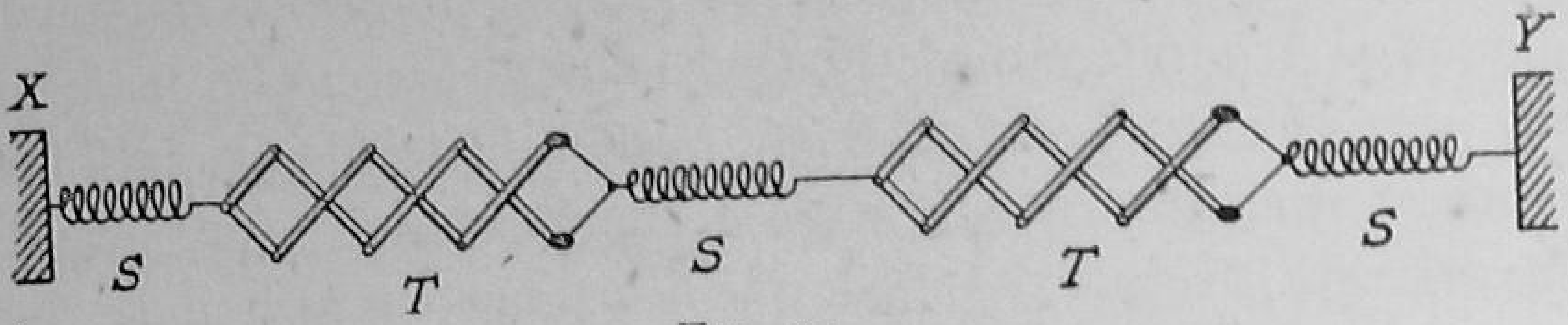


FIG. 29.

So much for the muscle fibril; we must now design a model of the A.T.P. molecule with its "high-energy" phosphate. Imagine two knobs of metal E and F (Fig. 30), one of which slides on a rod fixed into the other. The rod carries a spring H which is compressed as the knob F is pushed towards E. Because of this spring, F would not stay in position were it not for the presence of a catch G mounted at the end of the rod (which operates like the catch in an umbrella that prevents it from closing when opened); when this catch is depressed, the spring forces the two knobs apart. This catch expresses the fact that A.T.P. is a stable molecule under ordinary conditions, and the sliding knob, together with the spring, represents the "high-energy" phosphate. Here, then, is our source of energy; now we bring it into action. The two knobs of our model A.T.P. fit easily between the tong handles C and D (Fig. 31); but the tong handle C, as it closes on the knob E, depresses the catch G. The knobs separate violently, the handles are forced open, the tongs contract. Either the length of the whole structure decreases, or, if the ends are kept fixed, the springs are extended and the structure exercises a tension on the terminal attachments.

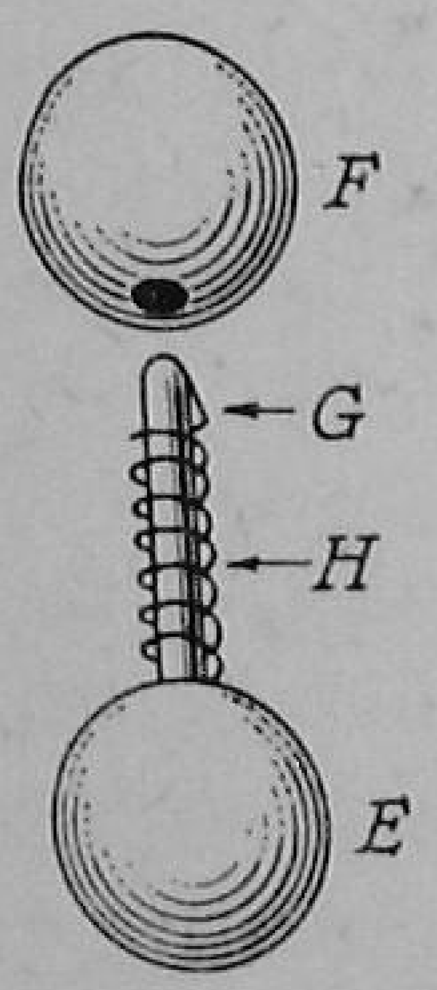


FIG. 30.

The depression of the catch by the tong handle is not a purely arbitrary detail of the model: it symbolizes the known ability of the myosin-actin-enzyme complex to promote the splitting of "high-energy" phosphate from A.T.P.

A molecular structure which would possess the two fundamental properties of the tongs, which would contract when certain groups within it are separated, and which, moreover, after the fashion of a lever, would convert a small movement into a much greater one of weaker force, would no doubt involve some ingenuity in design but no fundamental difficulty. The possibilities in fact are so numerous that speculation about detail is of little benefit in the present state of our knowledge.

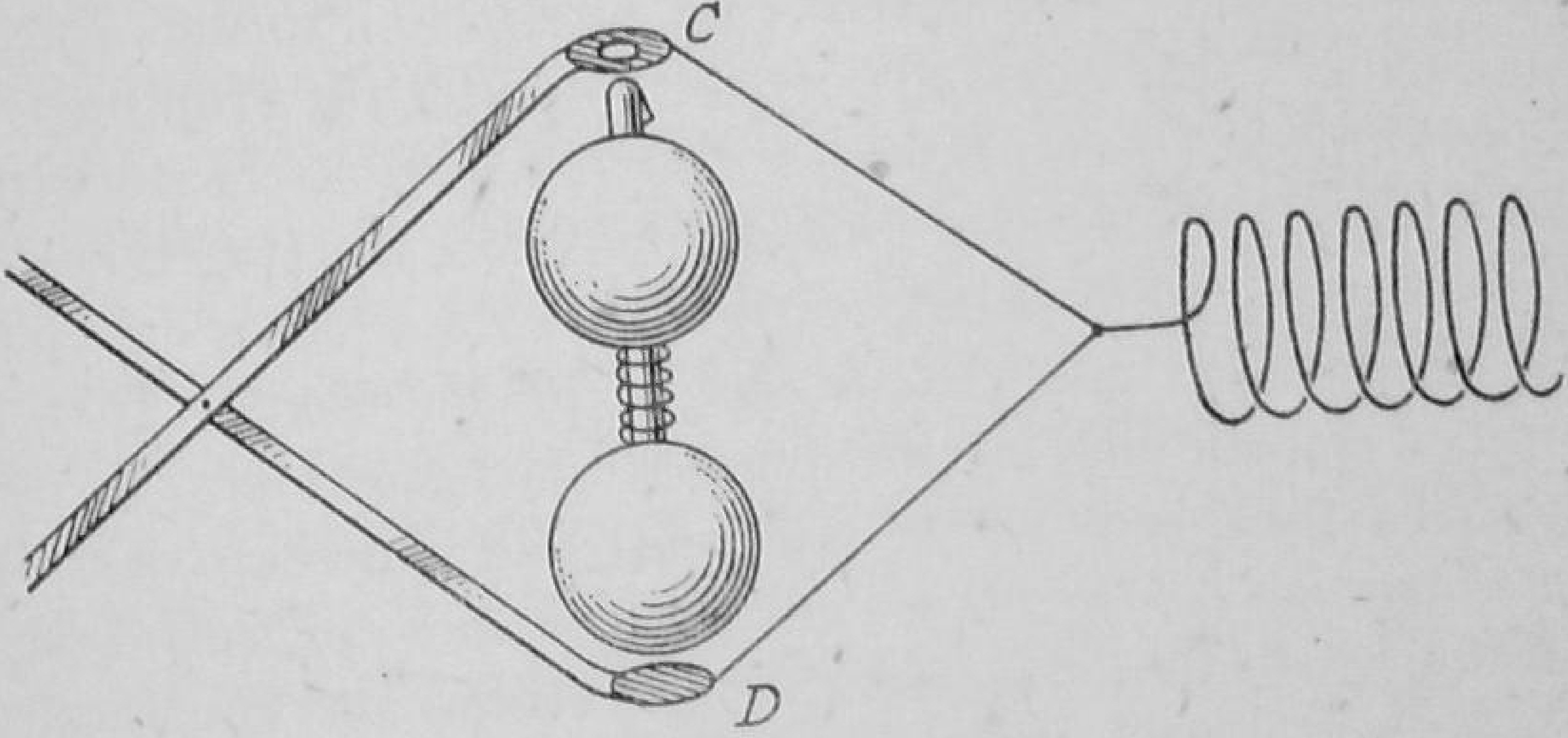


FIG. 31.

When the tongs had contracted, the separated knobs would be relatively free and would presumably separate from the handles in the form of phosphate and the residual part of the A.T.P. The tongs would be free to expand again and the muscle would relax. If fresh A.T.P. were available another molecule would engage the tong handles and the process of contraction would occur once more. Now an unstimulated muscle fibril, even in presence of A.T.P., does not contract: this may be ascribed in our model to some inability of the knobs to engage properly into the handles unless the electric charge they carry is just right. The attachment of A.T.P. to the myosin complex is known to be very sensitive to the presence of ions in the surrounding water. It is also known that in consequence of the A.T.P. fission and of other enzymatic chemical changes which accompany it, the ions in the surrounding water are significantly altered. Thus, a contraction

initiated at one point by a chemical change may be propagated to neighbouring points in consequence of the ionic alterations induced locally.

And now a word about the springs (S). These make the development of strain as opposed to actual contraction easy to understand. The springs presumably represent some kind of elastic protein fibres. The fibrils in ordinary voluntary muscle exhibit minute striations (see Plate II), and it is just possible that these reflect the existence of alternate "springs" and "lazy-tongs". The bands, about one-thousandth of a millimetre in breadth, are of two types, A and I, which alternate with each other, and when the fibril is stimulated, the length beiog kept constant, the A bands contract, but the I bands expand, just as the tongs and the springs do in our model. In the so-called smooth muscles, the muscles which are found in the internal organs, such as the intestines, and which are outside our voluntary control, there are no striations on the fibrils, and this would seem to mean that the elastic and contractile elements are not localized to the same extent.

All the individual processes in this enormously complicated mechanism which we call muscle are accurately controlled by enzymes, and whenever we wink an eye or snap a finger, a whole set of such mechanisms is set in motion all precisely harmonized with each other. When we contemplate the degree of control and co-ordination of the muscles which is demanded in any delicate operation, we are impressed by the complete perfection of the machine. But when we see the supreme achievements of muscular activity, a Pavlova dancing, a Davis controlling his billiard ball, a King's prizeman shooting at Bisley, then we can only wonder and admire. The more we analyse the situation, the more we realize the rigour of the standards of precision implied by such feats of human performance. Nature's engines are indeed miracles of design and construction; their existence would be incredible if they were not so utterly commonplace.

CHAPTER XI

NOT BY BREAD ALONE . . .

FOLLOWING the Second World War, hundreds of millions of human beings in Europe and Asia have been faced with famine. Hunger and starvation have become terrible realities to populations who had previously taken for granted their supply of bread, or potatoes or rice, and had scarcely imagined it could ever be otherwise. In such conditions of famine it is the basic supply of two or three thousand calories, or rather the food to produce this amount of energy, that is lacking, and when absolute starvation of this kind is threatening, the lesser malady of malnutrition or under-nutrition must necessarily take a second place.

Apart from the periods immediately following a major war, famine conditions are nowadays scarcely known in Western Europe, and they are even less familiar to the inhabitants of the New World. However, in the course of human history it is probable that in most countries the vast majority of the inhabitants have always suffered from under-nutrition. Even in this century, and during times of peace, it is far commoner than most people realize. In India and China, hundreds of millions eke out an existence on little more than a handful of rice a day. In the Europe of 1938, there was no lack of food, but many went hungry. In the United States, with its great agricultural wealth, there were many who suffered from malnutrition and even died from particular deficiency diseases. Food was then so plentiful in some parts of the world that it had to be burnt to get rid of it, and so scarce in others that millions languished or perished for lack of it.

The first problem in this matter of feeding the world is to produce enough food and of the right kind; the second is to distribute it where it is needed. The importance of a

satisfactory solution of this second problem is well brought out by the experience of Britain during the war. Over this period, food of almost every kind was distinctly short in supply. Total overall consumption had to be cut down. But all the available evidence goes to show that the nutrition of the people, and especially of the children, was better than it had ever been before. The infantile death rate fell, the average height and weight of school children rose. The rationing system was carefully thought out and efficiently administered. In consequence, everyone could have a sufficient supply of all the factors in his food that he really needed. Bread and potatoes were unrationed, and with the help of generous subsidies were kept low in price, so that everyone could have all the calories he wanted, and very cheaply. Some might complain of monotony in the diet, but none went hungry. This planning of food distribution was an essential step towards final victory in the war.

The post-war world is confronted with the short-term problem of saving millions from immediate famine, and the long-term problem of developing food production and organizing distribution so that everyone will be adequately fed whatever his race or country or social status. To this end the Food and Agricultural Organization of the United Nations has been formed. Time will show what degree of success this organization will achieve. The problem is in part technical, but also in part political. The agricultural and nutrition experts of U.N.O. can tell the world how to feed itself, and how to make sure that everyone has enough; but it is difficult to see how, in the absence of effective world government, it is possible to ensure that any plan can be carried out. To be effective, the central organization must have executive power; but here we meet face to face the cardinal problem of the limitation of national sovereignty. Here the problem is no longer technical or scientific; human emotions and prejudices and deep-rooted irrational ideas are involved. But the scientists and technical experts can help. They can clear the

ground; they can work out what will have to be done if the world is to be properly fed; how much food is required, where and in what manner this food would be best grown, and what factors are at present holding up its production and distribution. The human race, if it is wise, will listen to this advice and put it into execution. In this way a day may come when every man, woman, and child will be assured of the first condition of a free and happy life, the certainty of an adequate diet.

But what do we mean by an adequate diet? The primary purpose of foodstuffs is to supply the organism with energy. This it converts partly into mechanical work and partly into heat. We have seen in the case of an adult man that energy requirements depend on the amount of work which he does. His diet, to be adequate, must in the first place be able to supply him with this energy—rather less than 2,000 Kilocalories per 24 hours if he is resting in bed, possibly over 4,000 Kilocalories if he is engaged in heavy manual work. This consideration of energy requirements is absolutely fundamental in any discussion of the adequacy of diets. The necessity for the intake of a certain minimum number of Kilocalories is a direct consequence of the law of the conservation of energy, a law which the animal body must obey like any other engine.

But the animal body is an engine of a very peculiar kind. In the nature of things it has tasks to perform which do not fall to the lot of an ordinary engine. It must keep itself constantly in repair. Like other engines, its parts tend to get worn; but unlike them it cannot obtain spare parts ready-made from outside. It must constantly be making good by its own efforts all the wear and tear which its daily activities produce. We must remember, too, that these activities are going on without interruption during the whole lifetime of the animal. Ordinary engines are stopped periodically and now and then they are overhauled and thoroughly cleaned. The animal body must contrive to do all this while the mechanism is still running. Besides carrying on its normal activities, it must also

be prepared to meet emergencies, to repair any gross injuries, to adjust itself to an unfavourable environment, and to deal with any invasions by bacteria or other foreign intruders. It must have means at hand which it can mobilize to meet such a crisis. Certain diets may be adequate as long as the going is good, but they may not enable the organism to resist an attack of disease. Finally, in animals we have the special strain of reproduction and growth.

It is not surprising that these unique activities entail special dietary requirements, and it is during the periods of reproduction and growth that the problem of correct diet is most urgent. Not merely energy, therefore, is required from the food. Spare parts, lubricants, and the wherewithal for growth and reproduction are no less essential.

It is convenient to divide these supplementary dietary factors into three groups. There are, first of all, certain elements and simple inorganic substances such as iron and copper, sodium chloride, and calcium salts—these are indispensable constituents of the animal body and must be present in the diet. Secondly, there are various organic substances which the body is apparently unable to synthesize from simpler compounds, but which it requires in considerable quantities in order to build up its essential structures; the chief members of this group are certain amino-acids. Thirdly, there is a number of organic compounds which are also indispensable for the smooth working of the animal organism, but which are required only in quite small quantities. These substances, commonly called vitamins, may be regarded as somewhat analogous to the lubricating oil of the mechanical engine. The distinction between the second and the third class of compounds is not a very clear-cut one, but for practical purposes it is convenient to separate them into these groups.

The first class is the simplest to begin with, the elements and inorganic compounds. The number of elements which are essential for the proper functioning of living cells is surprisingly great.

For long it has been known that, apart from carbon, oxygen, hydrogen, and nitrogen, many common elements such as sodium, potassium, chlorine, iron, phosphorus, and calcium are important constituents of the animal body. As knowledge of the composition of tissues extended, it was recognized that a number of other elements were present, though in quite small amounts; in this category are included copper, magnesium, manganese, cobalt, and iodine, but the complete list would be a lengthy one, and it is probable that even at the present time our knowledge of the essential elements is still far from complete.

In the case of most of these elements it does not often happen in practice that a serious deficiency occurs. Either they are so abundant in nature, as in the case, for example, of sodium and chlorine, that the animal, guided by its instinct, is able when deficiency is threatened to choose food of such a kind as to correct the defect; or else the quantities involved are so small that it is almost impossible for the minimum limit of intake not to be attained. However, for one reason or another it happens that this happy state of affairs does not always exist, and it is of interest to consider one or two instances where the simple lack of a particular element or simple inorganic compound may be the cause of widespread disease and suffering.

Most of us at some time or other have noticed persons affected with the disorder known as a simple goitre. This trouble manifests itself as a swelling of the neck, resulting from the enlarged condition of the thyroid gland which is situated there (Fig. 52). The disease occurs far more frequently in some districts than in others. It used to be very common in certain valleys in the Swiss Alps and in the Austrian Tyrol, as well as in other mountainous regions in various parts of the world. But it was not exclusively found amongst mountains; it was prevalent, for instance, in certain parts of Canada adjoining the Great Lakes and in some maritime districts of New Zealand. In its mild forms simple goitre is

not a very serious disease, but as the swelling develops grave inconvenience may be experienced as the result of compression of the wind-pipe and the other organs in the neck. Later, it may develop into myxoedema, a form of thyroid disturbance characterized by physical and mental sluggishness and general impairment of functional activity. Moreover, a certain number of the children born in badly goitrous areas are quite subnormal in their development. They are small in stature, weak

TABLE III.—THE RELATIONSHIP OF IODINE TO GOITRE

Village	Percentage of Population having Goitre	Parts per Thousand Million of Iodine in:				
		Milk	Eggs	Water	Rocks	Soil
Effingen .	1	276	215	2–3	5,000–9,000	12,000
Hunzenschwill	56	85	80	0·04–0·25	300–700	600
Kaisten . .	62	73	147	0·5–0·8	400	800–2,000

Adapted from the results of Th. von Fellenberg (*Biochemische Zeitschrift*, Vol. 152, p. 141, 1926).

in body and in mind. In the worst cases the mental capacity of these cretins (as they are called) is extremely low and they are quite incapable of taking their place in the community. It was early recognized that cretinism and the prevalence of goitre are closely connected. It was not so easy, however, to detect the essential cause of these two diseases, and it is only during the present century that the mystery has been finally solved.

A clue is afforded by the data contained in Table III. The figures refer to three Swiss villages, Effingen, Hunzenschwill, and Kaisten. The second and third were highly goitrous; in the first the incidence of the disease was only slight. The outstanding point is that in the goitrous villages the iodine

content of the drinking water as well as of the vegetables consumed for food was very much less than in their non-goitrous neighbour. The suggested inference, namely, that simple goitre is the result of a deficiency of iodine in the diet, is supported by extensive surveys which have been carried out during the last two or three decades in Europe, America, New Zealand, and other parts of the world. Goitrous regions are found to be deficient in iodine; the soil, the drinking water, the vegetables, and even the animals all provide evidence of a general scarcity of this element.

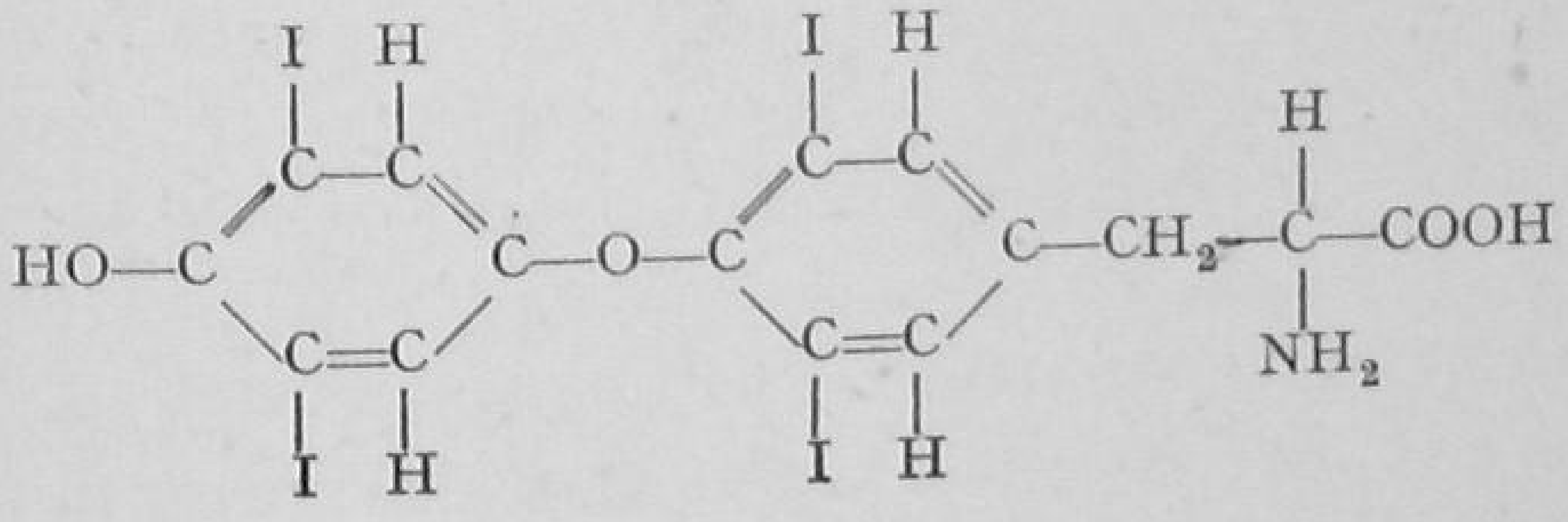


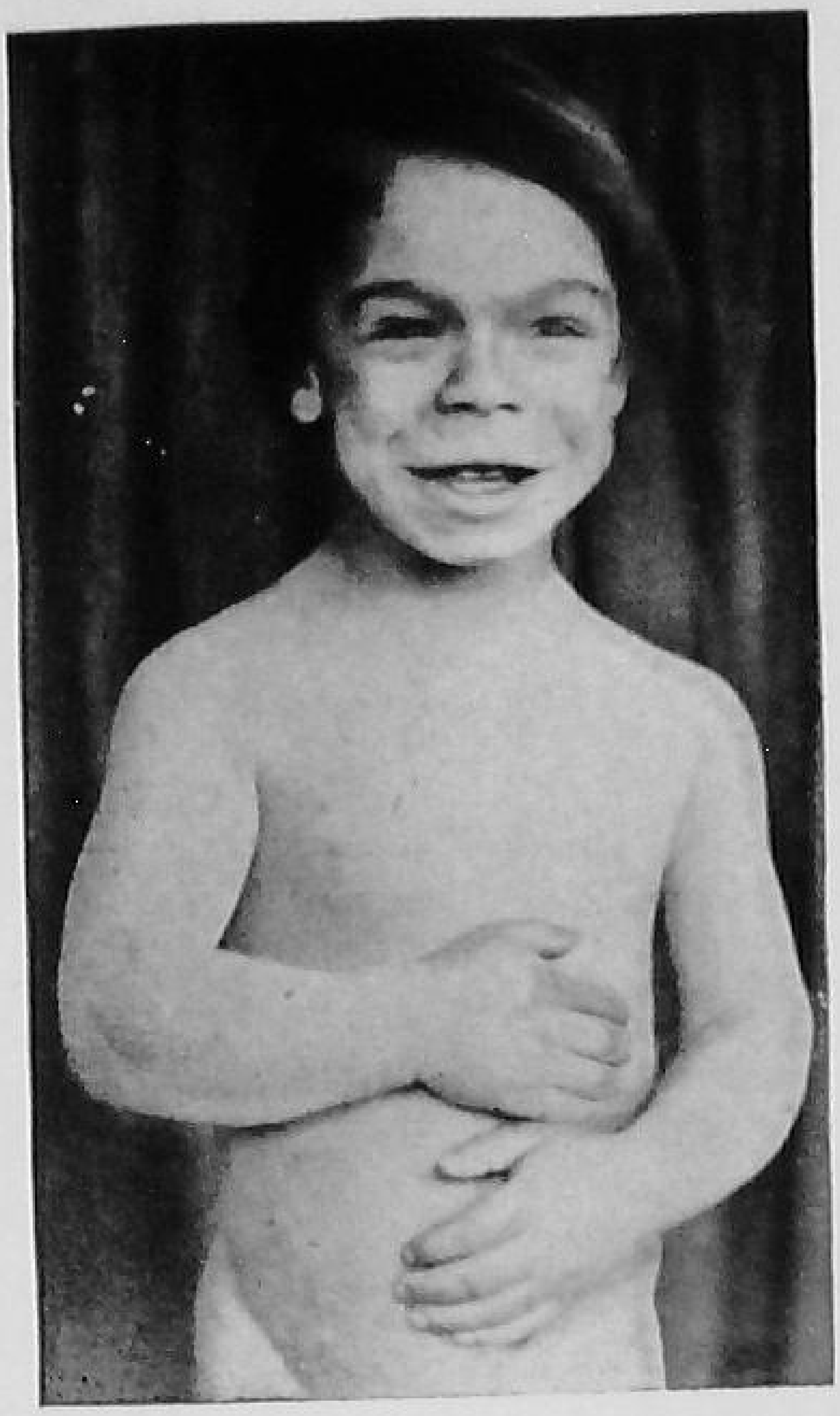
FIG. 32.—Thyroxine.

With our present knowledge of the function and chemistry of the thyroid gland, it is easy to understand the relationship between iodine deficiency and goitre. We now know that the thyroid synthesizes a compound called thyroxine, which contains four atoms of iodine in its molecule (Fig. 32). This compound, in combination with protein, is secreted into the blood-stream, whence it finds its way to the tissues. There it plays an essential role, for it regulates the speed at which the basic metabolic processes of the cells are carried on. When too much thyroxine is present everything is speeded up, nervousness and restlessness appear, and on the least exertion the heart palpitates alarmingly.

Sometimes the thyroid fails to function as the result of disease or it may have been removed completely by a surgical operation. In the course of a few months the state of the patient undergoes a dramatic change. The symptoms developed are just the opposite of those due to excess of thyroxine.

Physical and mental sluggishness set in, and the body generally, but more especially the limbs, become stout and appear somewhat swollen. The skin tends to become dry and brown, and the hair falls out. The discovery was made in 1891 that all these symptoms rapidly disappeared and the patient recovered practically normal health as the result of the administration by mouth of sheep's thyroid. This discovery was an event of great importance in the history of medicine, for it not only brought relief to many patients suffering from a distressing disease, but marked the beginning of a new epoch in the treatment of disease. It was later found that the thyroid was only one among many organs producing compounds essential to the well-being of the organism and emptying their secretions directly into the blood-stream. It has been found possible to prepare many of these active compounds in a form suitable for administration to the human patient, and so one by one new and effective methods of treatment have been developed for various diseases due to deficiency of these particular secretions (see Plate III).

However, it is only in the case of the thyroid gland that defective activity can be caused by a dietary deficiency. This is due to the accident that the somewhat rare element iodine forms an essential part of the active compound which the thyroid gland supplies to the body. The amount of iodine normally present in the food and drink of an ordinary man is probably of the order of a milligram per day—quite ample for his needs, but not sufficient to afford a very large margin of safety. It follows that where there is a considerable diminution in the amount of iodine in the soil and waters in the neighbourhood, there is the possibility of the development of a real iodine famine. This is, indeed, what happens in the goitrous areas. Soil, water, plants, all show a subnormal content of iodine. Animals suffer as well as man. Sheep, cows, pigs, and other domestic animals develop enlarged thyroids. The very fish in the lakes and streams exhibit the same symptoms of the ubiquitous disease. In the absence of a



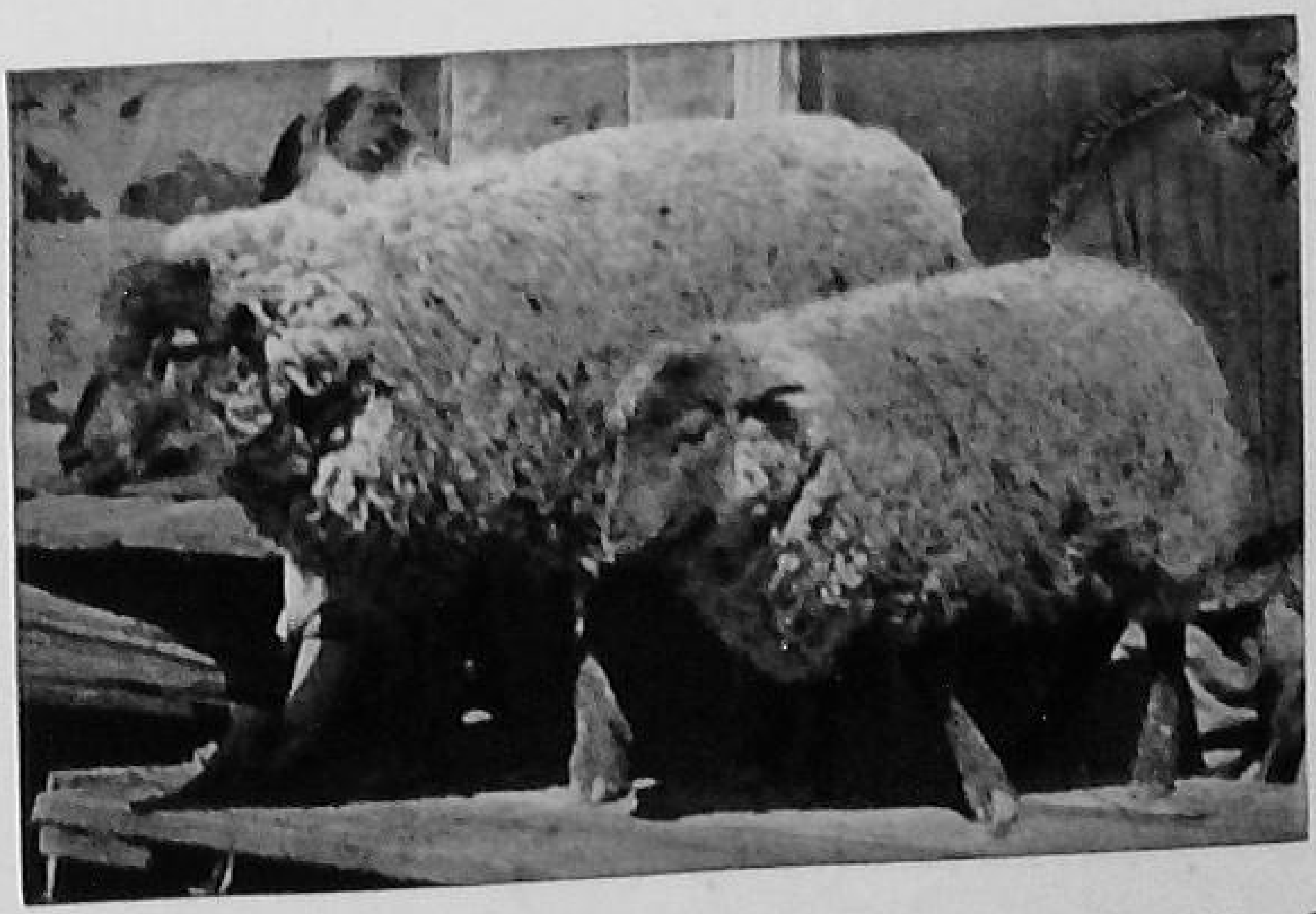
Cretin.

(From Garrod Batten Thursfield and Paterson "Diseases of Children.")

Effect of Thyroid Treatment on Advanced Myxœdema.

After two month's treatment with Thyroid he had lost twenty per cent of his initial weight.

(From Hertoghe "The Practitioner.")



Cretin lamb about one year old with normal lamb of eleven months.

SHOWING THE IMPORTANCE OF THE THYROID GLAND.

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sufficient supply of iodine, the thyroid gland is unable to respond normally to the demands of the body for the all-important iodine-containing compound, and it endeavours to make up for its incompetence by an increase in size. The resulting unhealthy overgrowth produces the swelling in the neck characteristic of the disease.

If goitre is so simply caused, it is just as simply prevented and cured. All that is necessary is to make certain that the populations of the goitrous districts, and especially young growing members of these populations, receive an adequate supply of iodine. It does not seem to matter very much in what form it is given as long as sufficient amounts of the all-important element are available to meet the needs of the body. In Switzerland the authorities distribute to the school children chocolate containing either sodium iodide or a suitable organic compound of iodine. In some countries iodide is added to the cooking or table salt sold in the affected districts. By these means the incidence of goitre has been reduced drastically in many parts of the world in which it was once prevalent. Individuals already affected by the disease may, of course, be cured by the administration of iodine. The swelling disappears within a week or two and the patient becomes entirely normal in health.

The prevention of goitre by iodine is not only simple, it is also very cheap. The dose required is but a few milligrams per week. Ten shillings' worth of sodium iodide would suffice a whole village of a couple of thousand souls for a year. Knowledge and administrative efficiency are here of much more importance than finance, for the cost is trifling even to the poorest community. Already goitre in its more serious forms, and especially its tragic accompaniment, cretinism, has been virtually wiped out in most of the civilized world. Nevertheless, in 1944, the Medical Research Council estimated that no fewer than half a million school children in England and Wales had neck enlargements indicating a shortage of iodine, a state of affairs which seems to indicate an unfortunate

failure of administrative efficiency, even though not necessarily involving any serious menace to health.

Thyroxine was prepared synthetically by Harington and Barger in 1936: this great achievement was accomplished by the laboratory methods and special tricks of the organic chemist and no attempt was made to imitate the milder but more mysterious processes followed by nature in the thyroid gland. It seemed fairly certain that in the thyroid, thyroxine is formed from the amino-acid tyrosine which already contains a large part of the thyroxine molecule in its finished form. Now tyrosine is a common constituent of proteins, and when proteins are treated with iodine under suitable conditions, they absorb this element, forming iodoproteins, in which most of the iodine is taken up by the tyrosine. Before the nature of the active principle of the thyroid gland was understood, it was known that the iodine in that gland was contained in a special protein called thyroglobulin, and the idea naturally occurred to various investigators that some of the common proteins if converted into iodoproteins by treatment with iodine, might develop the characteristic activity of thyroglobulin. All attempts, however, to produce active material in this way were unsuccessful, and when the structure of thyroxine was revealed, it seemed that the nature of the reactions involved in the conversion of tyrosine into this iodine-containing compound, though simple and straightforward on paper, could scarcely be expected to work in a test-tube.

Everyone was therefore very surprised when Ludwig and von Mutzenbecher announced not only that by iodinating casein they had obtained an iodocasein with thyroid activity, but also that from this iodoprotein they had succeeded in separating pure thyroxine. Yet Harington and others soon confirmed their results. A little later von Mutzenbecher showed that a solution of di-iodotyrosine kept for several days in sodium bicarbonate solution was to some slight extent converted into thyroxine. This result shows that in spite of

the inherent improbability of the reaction, di-iodotyrosine is, in fact, converted into thyroxine under the conditions of temperature and mild alkalinity obtaining in the body tissues, and without the need of any special enzymes.

We can now suggest a fairly plausible picture of how the thyroid gland manufactures thyroxine. This gland is in the first place a device for concentrating iodide, removing it from the blood-stream and accumulating it. At the same time it is oxidized to free iodine ready to act on the proteins produced in the gland. The production of suitable proteins would seem to be the second function of the thyroid. The iodination of these and the conversion of the tyrosine through di-iodotyrosine into thyroxine could then take place in a way analogous to the chemical processes revealed by von Mutzenbecher's experiments.

Apart from its theoretical implications, this work seems likely to lead to useful practical results. The iodocasein originally produced by Ludwig and von Mutzenbecher was fairly weak in its thyroid activity, but it was later found, both in Germany and in America, that incubation of the iodinated product for several hours at 80°C. results in a very substantial increase of its physiological activity and its thyroxine content. Specimens of iodocasein prepared by Reineke are said to have more than three times the physiological potency of ordinary powdered thyroid glands. The product seems to be pharmacologically equivalent to the natural substance, and it should be much cheaper to produce, and also be of a much more uniform quality. It may therefore come into clinical use for treating patients suffering from thyroid deficiency, and indeed we are told that such preparations of iodocasein were made in Germany during the war and used to eke out the small supplies of the natural hormone preparations.

Another element which the animal body cannot dispense with is iron. This metal is an essential constituent of the red pigment haemoglobin which performs the important function of carrying oxygen from the lungs to the tissues. In the

absence of a sufficient supply of iron, a shortage of haemoglobin inevitably develops: the bone marrow is no longer able to perform its function of building new red blood-cells. Consequently, a state of anaemia develops; that is to say, instead of about six million red blood corpuscles per cubic millimetre, the blood may contain four or even only two million. The transport of oxygen to the tissues in these circumstances is naturally very difficult, and chronic ill-health is the result.

An adult man requires to absorb about 10 milligrams of iron per day in order to make up for that lost by excretion and so prevent the development of anaemia. Most foodstuffs contain iron to some extent, but it is now generally agreed that for practical purposes only iron in the simple inorganic form need be considered, since iron in organic combination can only be utilized with difficulty if at all. In some foodstuffs half or more of the total iron exists in combination with certain of the organic constituents. In cereals over three-quarters of the iron is in this category; but on the other hand practically the whole of the iron in white fish is available, for it exists almost exclusively in the inorganic form.

With an ordinary mixed diet it may be taken that two-thirds of the total iron is available for absorption. It follows that the total iron consumed in the food must be substantially greater than the 10 milligrams per day mentioned above. There is a reason to believe that anaemia resulting from insufficiency of iron in the food is not very uncommon, and it is the opinion of some authorities that in the development of chlorosis, an ailment so common amongst young women a generation ago, simple iron deficiency was an important factor in the production of the bloodlessness characteristic of this disease. Fortunately it is a simple and inexpensive matter to remedy any suspected deficiency. There is no need to indulge in the costly patent medicines so widely advertised; all that is necessary is to take a trace of an iron salt (*e.g.*, ferric ammonium citrate) every morning, and this treatment should not cost more than a penny or two for a whole year.

Copper is another element, lack of which is associated with anaemia, but the role played by this metal in the body is rather more obscure, and the story of its elucidation is a rather interesting one. In most parts of the world young rats can be reared without difficulty on a diet of pure cow's milk. However, it was accidentally found that in certain districts of the United States young rats so nourished developed a very marked anaemia. It was then discovered that the milk used was unusually deficient in copper. In most parts of the world ordinary cow's milk contains a trace of this metal, but in the particular districts of the United States where the milk was inadequate for the nourishment of young rats, copper was almost entirely absent. This peculiarity was traced to a deficiency of copper in the grass on which the cows fed.

The addition of small quantities of copper sulphate to the milk diet of the rats produced an immediate improvement and eventually abolished the anaemia. At first it was doubtful whether the active substance was really copper and not some impurity contained in it, but the fact that even after the most careful purification, copper was still active, appeared to prove that that element was indeed the important substance. However, for some considerable time controversy raged over the question as to whether other metals as well, such as nickel or manganese, might not also protect against this form of anaemia. The difficulty was an experimental one; it was not easy to be certain that traces of copper were not contained in the substance to be tested or perhaps introduced accidentally in some other way, as from the fittings of the cage. The general conclusion from a large amount of work would seem to be that certain other metals are also active, but only when administered in considerably higher quantities than in the case of copper. There is little doubt that shortage of copper is the primary trouble in "milk anaemia".

The relation between copper and iron in the formation of haemoglobin is an interesting one. In view of the very minute amounts of copper involved, it is natural to suppose that this

metal behaves more like a lubricant in the process of haemoglobin formation than as an actual constituent. When anaemia develops in rats in consequence of copper deficiency, the iron is found to be stored up in the liver and spleen. If, now, small quantities of copper are administered to the anaemic animals, new red blood cells are rapidly produced and the stores of iron are correspondingly used up. Evidently the copper makes possible the utilization of the iron for haemoglobin formation.

But perhaps it is in the rearing of farmstock that the importance of traces of metals in the diet has chiefly shown itself. It is now many years since it was demonstrated by the workers at the Rowett Institute that in certain circumstances young pigs which were sickly and languishing became healthy and vigorous if only they were given adequate supplies of iron. More recently it has been found that Gingin disease, scientifically known as Enzootic Ataxia, a cause of high mortality amongst lambs in certain districts of Australia, is due simply to a deficiency of copper in the pasture, due in turn to a lack of copper in the soil of the affected areas. Simple dressing of the ground with copper salts or the administration of copper to the lambs or mothers in the form of suitable "licks" has resulted in the saving of millions of pounds to the farmers concerned.

An analogous disease has also been recently elucidated in Australasia. The malady, known as Bush disease in New Zealand, and Coast disease or Enzootic Marasmus in Australia, has been the cause of grave anxiety and heavy financial loss to sheep farmers in the stricken districts. A few years ago an energetic attack was begun on the problem, and now it has been found that the land where the disease is rife suffers from a lack of cobalt. Complete cure and prevention follow the introduction of "licks" containing that element. No doubt there are still many similar cases of deficiency yet to be discovered.

Even more widespread probably is the incidence, not of acute disease, but of poor health and stunted growth due to

inadequate supply though not absolute lack. The cure is simple and it is cheap, for the amounts required are so small as to cost very little.

Just as iron is necessary for the production of blood-cells, so calcium and phosphorus are essential for the development of bones. It is to be expected that the demand for these inorganic substances which go to the building up of the body structure will be most insistent and that the results of deficiency will be most disastrous in the rapidly growing young animal. This is indeed the case; but it must not be overlooked that there is also a particularly great demand for these substances during the periods of pregnancy and lactation. If this demand is not satisfied, serious consequences may result. In India, where dietary deficiency is common, it not infrequently happens that a pregnant mother develops a great thinning and weakening of the bones as the result of calcium and phosphate being mobilized in order to supply the needs of the developing child. In the case of cows a condition called "milk fever" sometimes develops during the early period of lactation, which used to be the cause of serious loss to farmers. In these days of high milk yielders a cow often supplies over three gallons a day. Such a cow might lose more than fifteen grammes of calcium in a single day, which would be six times the total quantity of calcium contained in its blood. Evidently, then, the drain on calcium may be very great and it is not surprising that the cow is not always able to mobilize its reserves quickly enough after the onset of lactation to prevent a serious fall in the calcium concentration of the blood. Now such a fall may have grave consequences for the animal. If, for one reason or another, it occurs in a human being it results in collapse accompanied by involuntary movements of a twitching, convulsive nature. The cow in milk fever collapses and exhibits the spasmodic movements typical of calcium deficiency. If the illness is sufficiently prolonged and intense, the animal may die. On analysis the calcium content of the blood is found to be abnormally low. Spectacular recovery is

brought about by the simple procedure of injecting a solution of a suitable calcium salt (usually calcium gluconate) into the blood-stream so as to make good the deficiency.

It is an interesting fact that in the days before the exact nature of this disease was known, it was found empirically that inflation of the udders of the affected cow with air was often successful in curing the animal. This treatment presumably acted by preventing the manufacture of milk in the mammary gland, thus stopping the drain on the blood calcium and making it possible for the deficiency to be met from the calcium reserves of the animal. However, this method was a troublesome and painful one, and the new treatment constitutes a very important advance in veterinary science.

Another case of deficiency developing under abnormal strain is sometimes met with in relation to sodium chloride. Salt has an importance in the body of a rather strange kind; it is contained chiefly in our blood, and it is there because the sea in which our primitive ancestors lived contained some salt (though not so much as it does now). Living animals are always trying to make themselves as independent as possible of their surroundings, and one of the earliest steps in this process was the establishment of a circulatory fluid of constant composition to bathe the tissues, and the simultaneous development of an impervious skin. The blood is thus an "internal sea". As such, the prime necessity is that its composition must not vary appreciably.

Now, miners and others who do heavy work in warm, moist surroundings, sweat enormously (several quarts per day) in the endeavour to prevent their temperatures rising. Sweat is essentially salt water and the miner develops a thirst and a desire for salt food. If both these natural cravings are satisfied together, all is well; but, thirst being the more urgent sensation, the miner is more immediately concerned to slake it, and the result is sometimes a condition of serious prostration accompanied by acute muscular pains called "heat cramps" or "miner's cramps". These cramps are due to water having

been replaced without the salt; and, indeed, the drinking of water containing about 1 per cent of salt prevents and cures the cramps as well as the prostration. This example shows how profound may be the disturbance brought about by a quite simple cause and how easy may be the remedy.

We may now go on to consider the second class of deficiencies, namely, those which result from the lack of certain organic compounds which the body requires in considerable quantities to build up new structures and make up for wear and tear. Certain amino-acids are the best-known members of this group. The fact that such compounds are indispensable is evidence of a certain limitation of the synthetic power of animal tissues. It is of some interest to consider this question rather more fully.

Generally speaking, we may regard the plants as the great synthetic chemists of nature. This is true not only of the higher plants, whose green colouring matter, chlorophyll, enables them to utilize the energy of sunlight for the purpose of synthesizing carbohydrates and other complex compounds from the carbon dioxide of the air, but it also applies to moulds and fungi and even bacteria (which are the simplest plants). Indeed, the synthetic activity of some of these moulds is truly remarkable. Some varieties of these primitive organisms, such as *Aspergillus* or *Penicillium*, are able to grow on a medium containing only inorganic salts and a simple organic compound such as alcohol or lactic acid as the sole source of carbon.

The micro-organism is able to synthesize from these simple starting-out materials all the complicated molecular structures necessary for its existence. Carbohydrates, fats of various types, proteins containing a wide variety of amino-acids, are all synthesized in the cells of these primitive organisms. Evidently these minute living bodies, which in the case of bacteria may measure only about 1μ (one-thousandth of a millimetre) in diameter, are able to effect triumphs of organic synthesis far beyond the wildest aspirations of the most

proficient human organic chemists of the present day. It is striking evidence of the complexity of even the very primitive types of living structure that this should be so.

When compared with these organisms of the plant kingdom, animals, and especially the more highly developed ones, are quite deficient in their powers of organic synthesis. It is true that they are able to build up complicated molecules of carbohydrate and protein, but only if they are provided with the right starting materials. They seem to be quite unable to synthesize certain units which are essential for the construction of molecules of particular proteins. Amongst these are included the amino-acids phenylalanine, tryptophane, and arginine. Certain of the other amino-acids can be synthesized from nearly related compounds, but not from much simpler substances. Thus, for example, there is some evidence that histidine can be synthesized from arginine and that an animal can survive without the former amino-acid provided that sufficient quantities of the latter are available in the food.

It is difficult to make any general statement regarding the synthetic powers of the animal organism, but it may be said that it is able to carry out many simple reactions which involve the removal of water from, or its addition to, an organic compound. In certain cases, too, it is able to effect the addition or removal of hydrogen or oxygen. Of course, with such reactions at its disposal it might conceivably be able to effect the synthesis of quite complicated structures. In fact, it is probable that in the plant the majority of the highly elaborate syntheses are effected through a series of simple steps of this type. However, the fact is that in the animal organism these reactions seem to be applicable only to a very limited extent.

At first sight we may perhaps be surprised that the more highly developed types of living matter are so deficient in synthetic power; but further consideration suggests that it is not really so strange after all. For plants, it is absolutely vital that they should be able to build up their own structures *ab initio*. Being rooted in the soil and quite immobile, they

can make use only of the compounds present in the ground and capable of being absorbed through their roots. This limits their sources of material to very simple inorganic compounds and to the carbon dioxide of the air. But animals are quite different. Chemically speaking, they are all parasites, which have learned how to absorb and utilize substances already synthesized in the bodies of plants or of other animals. Now it is a general rule of parasites that they lose their power of carrying out those functions which they rarely or never exercise. They become lazy and degenerate. And so the animal body, finding it easier to live on the product of other organisms than to build up the structures it requires, does not possess the ability to synthesize all the structures essential for its well-being.

This limitation in synthetic activity has several important consequences. All living tissues are constantly undergoing a certain amount of wear and tear. This is naturally greatest during periods of work and activity, but even during sleep it is far from negligible. Consequently the tissues must ever be repairing themselves, and they must either synthesize the spare parts required or obtain them from without. The chief constituent of most tissues is protein, and, if body equilibrium is to be maintained, there must be present in the food an adequate supply of protein-building constituents. In practice these are most readily available in the form of proteins of plant or animal origin. An average-sized adult requires at least 20 grammes of protein per day to make up for the losses resulting from ordinary wear and tear. In order to allow for extra requirements, occasioned, for example, by work and exercise, it is desirable that his diet should contain at least 50 to 100 grammes of protein. But it is not sufficient simply to include this minimum amount of protein in the food. If gelatin, for example, were the only protein eaten, even an unlimited supply of it would not prevent loss of weight and ultimate death; for this protein contains no tryptophane and, as we have seen, this is an amino-acid which the animal body

is unable to synthesize for itself. A number of other proteins are also deficient in one or other amino-acids, and hence alone they are unable to satisfy the animal's needs. This is more often true of vegetable than of animal proteins. It is, of course, only natural that the flesh of one animal should contain all the amino-acids necessary for the synthesis of the very similar proteins present in the flesh of another. Hence it is to be expected that on the average, any animal protein (apart from specialized types such as gelatin) will be more completely utilizable than a plant protein taken at random. However, on a mixed diet of pure vegetable origin which includes proteins of various types and from various plants, there is little likelihood of an amino-acid deficiency occurring, especially if the diet is a fairly liberal one. The need for an adequate supply of amino-acids is no argument against the adequacy of a purely vegetarian diet.

CHAPTER XII

THE VITAMIN RACKET

PERHAPS, after all, the vitamins are rather a fraud. This is not to say that they do not exist or that they are not important; on the contrary, there is no doubt but that we should all die if we did not consume them in sufficient quantities. But the whole idea of a group of peculiar substances called "vitamins" is a subtly misleading one. We are apt to associate with this word the notion of a number of mysterious, intangible principles, delicate essences, easily destroyed by heat or even by air. It is not so very long ago since some eminent authorities questioned whether vitamins really existed at all. In any case, they seemed to be things of a kind apart, and so strong was the impression they created of their peculiar nature that they were given a name all to themselves.

Now, in the first place, even if we allow for the moment that they have a claim to be considered as constituting a group of substances deserving of a special name, that name itself is a fraudulent, misleading one, for it was given on the assumption that these compounds were all amines (see p. 60). The fact is that some of them are amines, but others are not. It is true the word is now usually written without a final "e", and this partially atones for the unhappy choice, but the suggestion of misrepresentation still hangs about the word.

However, the more serious point is that the use of the name "vitamin" suggests that these substances form a natural group of compounds in some way distinguished biologically or chemically from all others. It was possible to support this idea as long as none of the so-called vitamins had been isolated nor even proved to be an ordinary chemical compound, but first one vitamin and then another was obtained in pure form and its constitution established. They turned out to be ordinary

chemical compounds, most of them not even specially unstable. They just happen to be compounds which the animal organism cannot make for itself, and since they are essential for the proper functioning of the body they must be supplied in the diet. But as we have seen, many other substances not usually called vitamins must needs be included in the diet if the animal is to survive in good health. The name "vitamin" was invented to denote a few of these necessary substances which at that time could not be isolated.

It is true that all the vitamins have this feature in common: that they are required by the animal organism only in very small amounts. But in a sense this merely emphasizes the point which has just been made. If any of these compounds had really been required by the organism in large quantities, it would probably have been isolated and identified at an early date, and for this very reason would not have been included among the vitamins. Thus, for example, the essential amino-acids might easily have been included among the vitamins if they had not already been known as definite chemical compounds. In any case, the smallness of the dose is, after all, a purely relative matter. Even one microgramme (a unit in which it is often convenient to measure doses of vitamins) which is one-millionth of a gramme or about one five-hundredth millionth of a pound, will contain about a thousand million million (1,000,000,000,000,000) molecules—rather more than one molecule for every cell in your body. Further, different vitamins differ quite widely in the order of dose required. Thus, the daily dose of vitamin B_1 required to prevent convulsions in pigeons is of the order of a few microgrammes, whilst for vitamin C, the factor which prevents and cures scurvy, the quantity required daily by guinea-pigs has to be reckoned rather in milligrams. And in respect of this latter vitamin different animal species vary widely in their requirements. Thus, to take an extreme case, rats appear to be able to live on a diet completely lacking in vitamin C. It is not that their tissues can really function without the

vitamin, but rather that it is synthesized within their bodies, either by some of their own organs or by bacteria within their intestinal tract.

There is still another difficulty with which we are confronted if we wish to retain the idea of the vitamins as a definite and well-defined group of substances. This may be illustrated by considering the case of vitamin A, one of the factors which are necessary for growth and for maintenance of the skin and mucous membranes in a healthy condition. Certain fish-liver

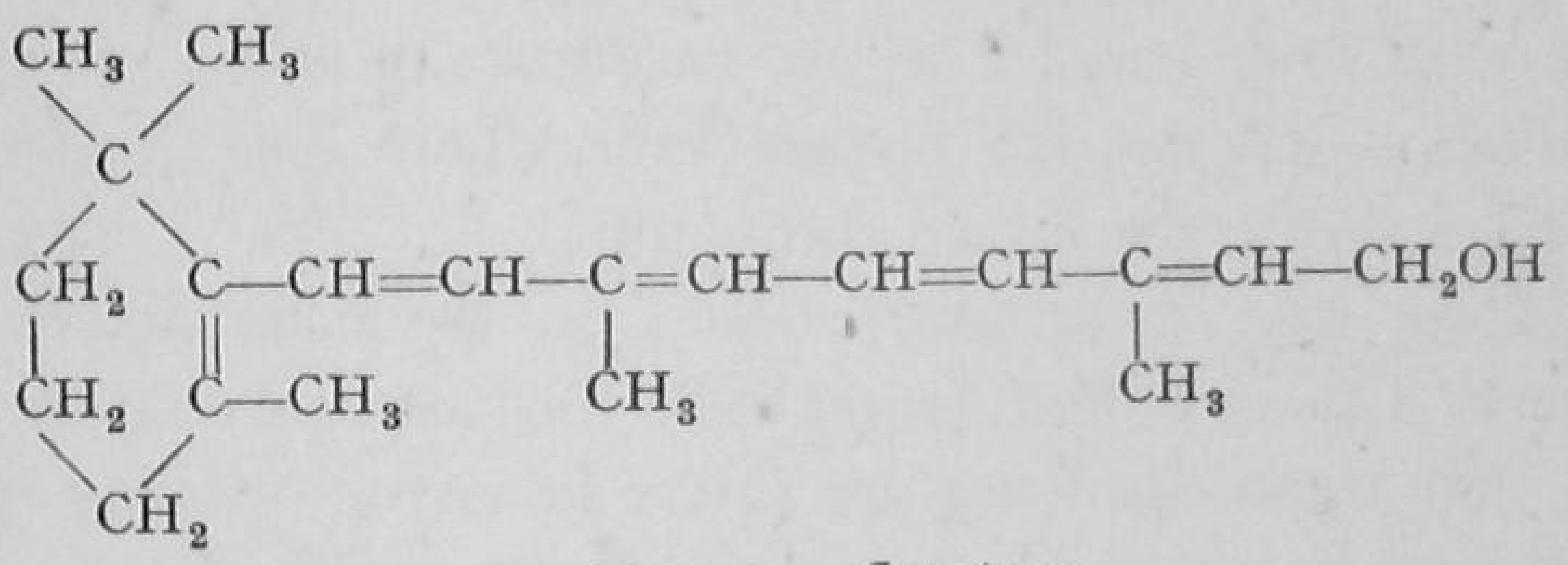


FIG. 33.—Carotene.

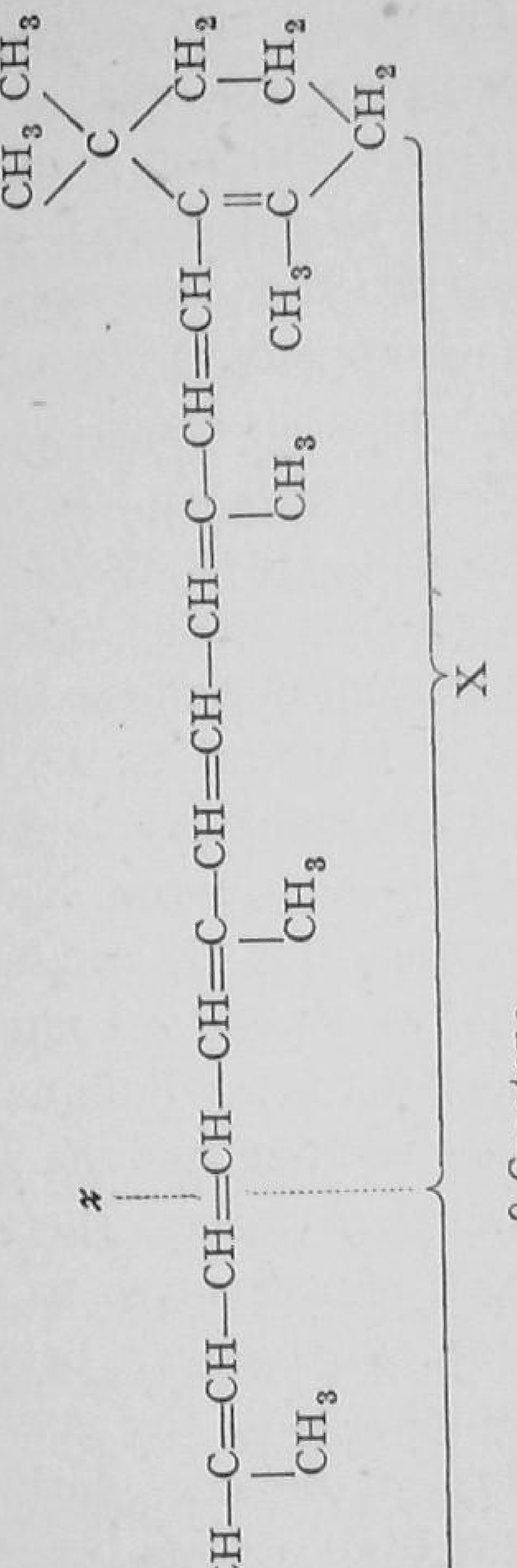
oils, for example, that from the cod and more especially that from the halibut, are very rich in this factor. From such sources a compound of extreme activity may be isolated of which the probable constitution is shown above (Fig. 33). However, it is not really necessary to have this compound at all, for it is found that its place may be taken by a much commoner substance called carotene. This red compound is widely distributed in nature, but was first isolated from carrots.

However, the doses of carotene which are required are larger than those of the compound isolated from the liver oils. The explanation becomes clear if we inspect the formula of carotene (Fig. 34: β-carotene) and compare it with that given in Fig. 33. It is evident that carotene would be converted into the more active compound if it underwent fission at the point marked *x*, for the two halves of the carotene molecule are very closely related to the structure shown in Fig. 32. It is therefore concluded that in the animal body carotene is converted to the

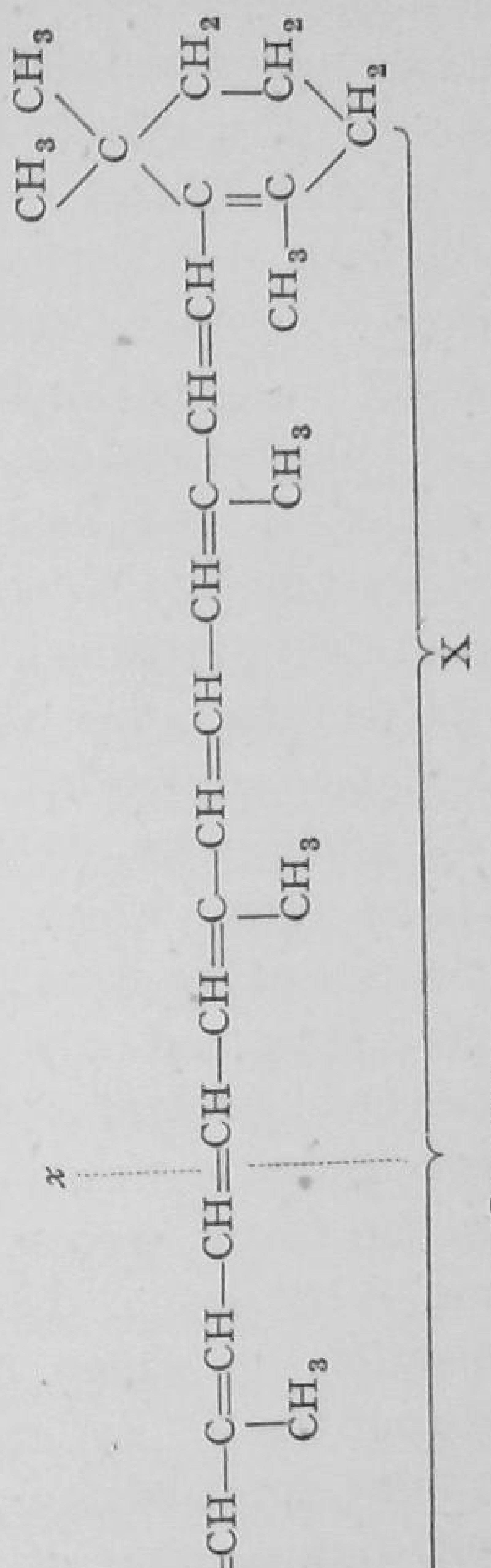
active compound. Some years ago the situation was found to be somewhat more complicated. Crude carotene was found to be a mixture of three chemical compounds. In each of these compounds the molecule may be regarded as made of two halves, but whereas in β-carotene the two halves are identical and both possess a structure precisely analogous to the vitamin, in α-carotene only one of the two halves is of this type, the other being somewhat different. The third component, γ-carotene, resembles α-carotene in being asymmetrical in structure, but is present in only small proportions and need not concern us further here. The two carotenes, α and β, may be represented as XX and XY respectively, where X is the group which gives rise to the active compound.

It follows that β-carotene should be twice as active as α-carotene. This is, in fact, found to be the case and so it seems certain that these carotenes are active in virtue of being converted into the compound present in the liver oils. Of course, both may be converted ultimately into some other compound still unknown—on this point we cannot even hazard a guess, for we do not know just how vitamin A produces its effects. It has been suggested that the name "vitamin A" should be retained for the highly active substance found in the liver oils, and carotene should be called a "provitamin".

Vitamin A is sometimes called the anti-infection vitamin, but this name is rather misleading. It is true that people suffering from a deficiency of this factor tend to develop a disease of the eyes known as Xerophthalmia, which is really a chronic infection of the conjunctiva, the delicate membrane lining the eye-lids and covering the eyeballs. So characteristic of vitamin A deficiency is this infection that the vitamin is sometimes called Axerophthol. However, it is really a secondary and in a sense an accidental effect of the poor condition of the mucous membranes, including the conjunctiva, which results from a lack of a factor essential to their healthy metabolism. They tend to become rough and scaly; the skin, too, may become dry and unhealthy with serious vitamin deficiency.



β-Carotene.



α-Carotene.

FIG. 34.—Formulae of Carotenes.

We do not know just how vitamin A helps to maintain the mucous membranes in a healthy condition and so resistant to infection; but more definite information is available about the part it plays in another connexion. Vitamin A helps us to see in the dark; it is more accurate to say that if we are suffering from a serious vitamin A deficiency, we cannot see in a faint light. To understand what happens, it is necessary to explain something about the mechanism of vision.

At the back of the eye is the retina on which the lens causes an image of the observed objects to fall. There are two sets of receptors in the retina which are sensitive to the light, and which when illuminated bring about stimulation of the nerves, with which they are connected, and so transmit to the brain details of the image; these receptors are called the rods and the cones. The cones, which distinguish between light of different colours, are the more numerous, but are unaffected by faint light. If we had only cones, we should see much as we do at present in sunlight or in good artificial illumination, but on a moonless night we should see nothing but the stars. It is in relation to the second type of receptors, the rods, that vitamin A comes in. The rods are sensitive to very faint illumination, but they do not distinguish between light of different kinds. We are familiar with the greyness which everything develops as the dusk approaches darkness. This apparent disappearance of colour from objects occurs as the light becomes too faint to affect the cones, and acts only on the rods.

As the rods are so sensitive to faint light, it is not surprising that they go out of action when the light approaches normal intensity, and leave everything to the less sensitive cones; otherwise the nerves might be unduly stimulated and the eye dazzled. How is this desensitization of the rods achieved?

In the rods is a pigment called visual purple, and the sensitivity to light is dependent on this pigment. It absorbs light and evidently undergoes some chemical change in doing so. But if it receives too much light, the change becomes

obvious, for the pigment bleaches. Investigation has shown that the visual purple is a combination of a special protein with vitamin A and that under the action of intense light this pigment is bleached. In the retina slow regeneration of colour takes place in the darkness, and the visual purple is restored.

We can now understand why people very deficient in vitamin A are unable to see in very faint light. Their supply of visual purple is deficient, one of its essential constituents being lacking; consequently their rods are out of working order—their cones, of course, are useful only in brighter light. We can also understand why we find it so difficult to see for some time after we go out of a brightly illuminated room into the dark. The bright light has bleached our visual purple, and for the time being we are like the vitamin A deficient man, without rod vision, though for a different reason. In our case, the visual purple is gradually regenerated if we remain in the dark, and in a few minutes we find we can see once more.

During the Second World War, a great deal of attention was given to the problem of improving the night vision of pilots and other service personnel engaged on night operations. At one time it was thought that liberal dosing with vitamin A was helpful, especially where night vision defects (so-called "night blindness") existed. Further experience cast doubt on this idea. With people on an ordinary mixed diet, it seems that failure of night vision is rarely, if ever, due to vitamin A deficiency. There are, in fact, other causes for the rods not acting properly, such as some congenital defect; and trouble of this sort is, of course, not rectified by vitamin A administration. It is only in definite vitamin A deficiency that night blindness is likely to be cured by giving the vitamin.

The fish-liver oils, which are our richest source of vitamin A, happen to contain also another vitamin, and it took biochemists many years to distinguish between these two factors, though they are now known to be completely unrelated, and to possess distinct chemical and physiological properties. This

second factor is vitamin D, and is essential for the prevention of rickets.

As the bones are composed essentially of calcium phosphate with a little carbonate, proper ossification is, of course, impossible unless there is a sufficient supply of calcium and phosphate in the diet. However, these are very inefficiently absorbed and utilized unless an adequate supply of vitamin D is also available. The story of the elucidation of the nature of this vitamin takes us back to the early days of vitamin research and is a good example of the roundabout route which science must sometimes follow in order to reach its goal.

After the First World War rickets was terribly common amongst the children in the cities of Central Europe. This was an aftermath of the malnutrition and privation which the catastrophe brought in its train. In Vienna, where conditions were very bad, it was discovered that exposure of the children to sunlight had a wonderfully beneficial effect. At about the same time it was demonstrated that cod-liver oil and also certain other natural products will protect children and young animals from rickets even in the absence of sunlight. The facts available suggested that cod-liver oil was rich in a rickets-preventing (anti-rachitic) vitamin, and that a provitamin existed in the tissues and skin of animals, capable of being transformed into the vitamin as the result of irradiation. Following up this line of investigation, it was found that the short (ultra-violet) rays are the active component of the sunlight, and it was soon established that it was sufficient to irradiate the food of an animal to save it from rickets. Further, when the different components of the food—fats, carbohydrates, proteins, salts, etc.—were separately treated, it was only the first which developed anti-rachitic power, and, indeed, only the small fraction which resists saponification. The search soon narrowed down to the well-known substance, cholesterol, and for a few months it was thought that here at last was the "provitamin". But then, to everybody's surprise, it was suddenly discovered that almost all samples of cholesterol

contained as an impurity a small but significant amount of a closely related substance, ergosterol. Pure cholesterol, it was found, could not be activated by irradiation: it was really ergosterol which gave rise to the anti-rachitic substance.

This line of investigation was crowned with success a year or two later, when the active compound, the vitamin, was isolated from the irradiated ergosterol in a pure crystalline form. It was called calciferol, and was highly active, the total dose (spread over ten days) required to cure a rachitic rat on a diet otherwise lacking in vitamin D being of the order of 0·5 microgrammes. The vitamin D problem appeared to be solved. But soon clouds began to appear on the horizon: it was found possible to separate from fish-liver oils a fraction actually more active (in certain animals) than pure calciferol. Could it be that more than one substance possessing vitamin D activity existed, and that calciferol, though certainly active, was not the most potent compound? This, indeed, proved to be the case, and it has been found that quite a number of compounds, all closely allied to ergosterol, give rise to active substances when irradiated by ultra-violet light. The most active product so far known is that obtained by irradiating an oxidation product of cholesterol. Thus, there are several compounds all of which can cure rickets, and all having therefore the right to be called vitamin D; corresponding to these there are several "provitamins"—all closely related substances. The active substances presumably all act in the same manner, although their activities differ in a quantitative sense.

When a number of allied compounds have the same physiological effect, but differ in a quantitative sense, the question at once arises as to whether the various compounds have each an independent action or whether there is really but one active compound and the others act only after they have first been converted into it. Sometimes this question is rather difficult to answer with certainty, as when the active compounds are so related that they might be expected to be readily convertible into each other *in vivo*. However, in the case of the various

compounds with vitamin D activity, easy interconvertibility *in vivo* is scarcely to be anticipated on chemical grounds in spite of their close relationship. It is more probable that anti-rachitic activity is a property of a whole class of related compounds which, being allied in structure, exhibit similar physicochemical, and therefore similar physiological properties.

The history of scurvy is intimately connected with the development of long-range navigation. It was only when Vasco da Gama sailed round the Cape to the East Indies in 1497, and so introduced that era when voyages of three, six, or even twelve months were the order of the day, that scurvy became the dreaded disease of the sea. The calamitous effects of this malady may be illustrated by reference to Lord Anson's expedition. Five Admiralty ships left England under his command in September 1740; of these but one returned after four years' absence, and brought back only 5 per cent of the original crew. Of the others the vast majority had died of scurvy. It was in 1795 that the institution of a ration of lemon juice practically abolished scurvy from the British Navy, but it continued to be rife in the mercantile marine for another seventy years, until in 1865 Board of Trade Regulations made the lemon-juice ration compulsory in this service also. Many descriptions of the disease have come down to us from the seventeenth and eighteenth centuries. We read of the terrible suffering of the men—how their gums became swollen and spongy and their teeth dropped out, their flesh bled internally, their bones weakened and fractured; how their strength was lost, and they were in constant racking pain, until at last death came, perhaps with dramatic suddenness after some minor exertion, perhaps as the result of an attack of some infection on the already weakened body.

Vitamin C may well be regarded as the senior of the vitamins. It is now two hundred years since Captain Cook realized how important it was to provide his crews with vegetables and fruit on their long voyages if they were to avoid scurvy. Though he did not know the word "vitamin" he appreciated

the point which was all-important practically. And this same anti-scorbutic factor was the first to have its constitution completely elucidated, and the first to be synthesized in the laboratory.

It is now over a quarter of a century since it became generally realized that this vitamin was relatively abundant not only in lemon juice, but in most fruit juices and in fresh green vegetables. These are our natural sources of this essential food factor. But, curiously enough, it was not from any of these materials that it was first obtained in a pure form. The story of its isolation by Szent-Györgyi from the suprarenal glands of animals, not as a vitamin but as an important factor in the processes of cellular oxidation; of his suspicion that this crystalline compound might be identical with vitamin C; the gradual conversion of this suspicion into certainty as more and more evidence accumulated; and finally his isolation of the substance in quantity from the juice of the red pepper (paprika) of his native Hungary—all this is a very interesting and remarkable story of long and laborious effort crowned with final success. But it is also a story which well exemplifies the international character of scientific research. For Szent-Györgyi himself worked not only in Hungary, but also in Britain and America; and the credit for demonstrating the identity of the suprarenal compound with vitamin C must be shared by him with the American biochemists C. G. King and W. A. Waugh, who reached the same conclusion almost simultaneously.

Although ascorbic acid, as this crystalline compound is now called, is without doubt largely responsible for the anti-scorbutic value of orange juice and other fruit juices, Szent-Györgyi himself has recently raised the question as to whether it is the only active factor therein. Amongst the disturbances characterizing scurvy is an abnormal permeability of the walls of the blood capillaries, but though cure is effected by the administration of fruit juice or green vegetables, yet according to this recent work pure ascorbic acid is not effective

Szent-Györgyi finds, however, that small quantities of certain non-nitrogenous constituents of plant tissues belonging to the group of flavones (for example, hesperidin, present in lemon juice) are able along with pure ascorbic acid to effect complete cure of the disease. In other words, hesperidin is really a vitamin and it (or an equivalent compound) is essential for the health of the capillary walls. Szent-Györgyi proposes to call this factor vitamin P, as it prevents abnormal permeability. In this case the constitution of the compound was known even before it was recognized as a vitamin.

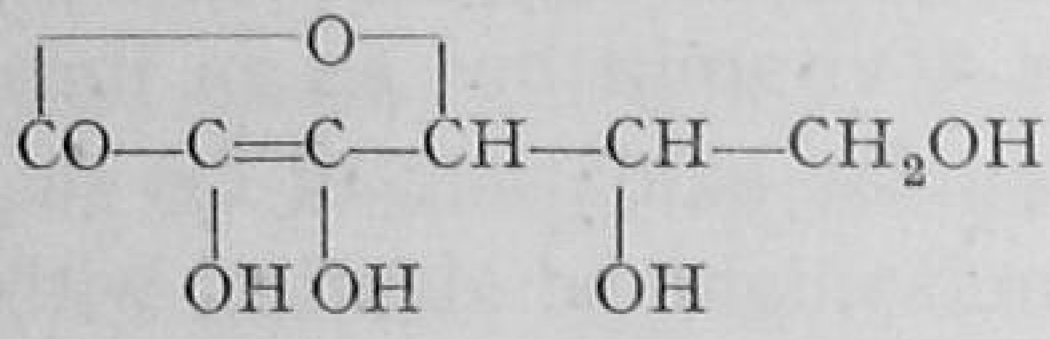


FIG. 35.—Ascorbic Acid.

Once ascorbic acid could be obtained in reasonable quantities, the way was open for an attack on the problem of its structure by the methods of organic chemistry. The struggle was a short but highly exciting one. The vitamin had contrived to lead the attackers off the scent by laying a false trail. It behaved like an acid and everyone assumed that it contained a carboxyl group. On this basis certain formulae were proposed and work on the synthesis of the vitamin begun. However, the help of the X-ray crystallographer was called in. Dr. Cox was able to assure his colleagues, Professor Haworth and Dr. Hirst, that the X-ray diagrams could not possibly be produced by a compound having any of the proposed structures. Indeed, no formula containing a carboxyl group would fit all the facts. And so the trick was found out, and it was realized that ascorbic acid does not really possess a carboxyl group at all. Having then cleared away this erroneous conception Haworth and Hirst suggested the true formula, according to which the acidic properties are due to a special configuration containing two hydroxyl groups as shown in Fig. 35.

But a very curious thing happened. Usually the final proof of the structure of a substance is afforded by its synthesis in the laboratory. Various workers had begun to synthesize the vitamin on the basis of wrong formulae, and the extraordinary thing is that one of these efforts was successful. For just before the correct structure was discovered, Reichstein, working in Zurich, announced the synthesis of the natural product. Haworth and Hirst, of course, were able to show that the synthesis by the route actually followed was in fact compatible with the new and correct formula, and they themselves effected

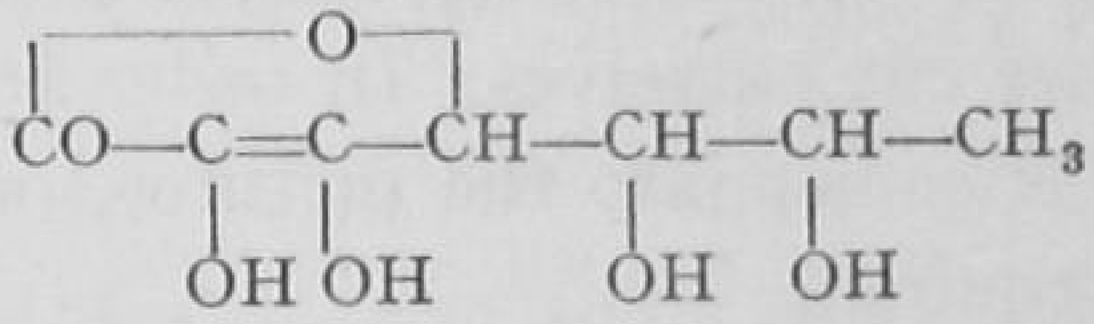


FIG. 36.

a similar synthesis independently. Nevertheless, it is a very unusual and almost unprecedented thing that the wrong formula should suggest the right method of synthesis. The wrong structure was, of course, fairly closely related to the right one, but even so the case illustrates how unexpected may be the snags which trip up the research worker.

Once the formula of the naturally occurring ascorbic acid was known, it became possible to prepare a number of closely related compounds and to find out whether these also possessed a vitamin C activity. It was found that some of them did, though in no case was the effective dose as small as that of ascorbic acid itself. The compounds which proved to be active all contained the ring system of ascorbic acid; minor changes which left the ring intact reduced, but did not abolish, the activity. Thus the compound represented in Fig. 36 can replace ascorbic acid, though five times the dose is required.

The same lack of exact specificity is shown by vitamin K. This vitamin is concerned with blood coagulation; when an animal does not receive sufficient of it, its blood fails to clot properly, and if it receives a wound which would normally be

trivial, it may bleed to death. We do not perhaps usually realize just how important and delicate a matter it is that the blood should clot just at the right place and time and never otherwise. It is a very serious matter if it clots in the course of its normal circulation through the blood-vessels; it is also serious if it fails to clot promptly whenever it finds itself escaping from these blood-vessels, for example, through a cut or other wound. It is not surprising to find that there exists a curious and somewhat complicated mechanism to bring about the everyday, commonplace result that is so vitally necessary to us all—no clotting till it is wanted: a prompt clot whenever we cut ourselves. In order to understand just where vitamin K comes into the picture, some notion of this mechanism is required.

Blood contains a protein called fibrinogen, and the essence of the clotting process is that this soluble protein is converted into the fibrous, stringy, insoluble fibrin—it is the felted strands of the fibrin which, entangling the red blood-cells, form the clot. The essential action, the conversion of fibrinogen into fibrin, is brought about by an enzyme, thrombin. Of course, it would not do if thrombin were present in the circulating blood, for then our blood would set in our veins. Instead of the active enzyme, we find in the circulating blood an inactive precursor, prothrombin. The prothrombin remains dormant as long as the blood is safe within the vessels. To activate it, two factors are necessary; calcium, and another not yet fully understood, called thrombokinase.

In normal blood there is always enough calcium to allow the transformation of prothrombin into thrombin; as it happens, however, one of the simplest and commonest methods of preventing clotting is to remove all the calcium from solution in the blood; for example, by adding potassium oxalate so that insoluble calcium oxalate is precipitated.

And now we come to the crux of the matter: what starts off this whole complex mechanism? What pulls the trigger at the right moment? The answer is that the second "activating"

factor, thrombokinase, is made available just when clotting is called for. There may be more than one type of thrombokinase; we know it is present in tissue juice: a nasty graze may bleed much less than a small razor cut, for the damaged cells in the grazed tissue are a good source of thrombokinase. But we also know that blood collected from a vein into a test-tube, making practically no contact with cut tissues, will nevertheless clot in the course of a few minutes. The explanation here is that thrombokinase is liberated from small particles called "blood platelets", by mere contact with a foreign surface —such as the wall of a test-tube.

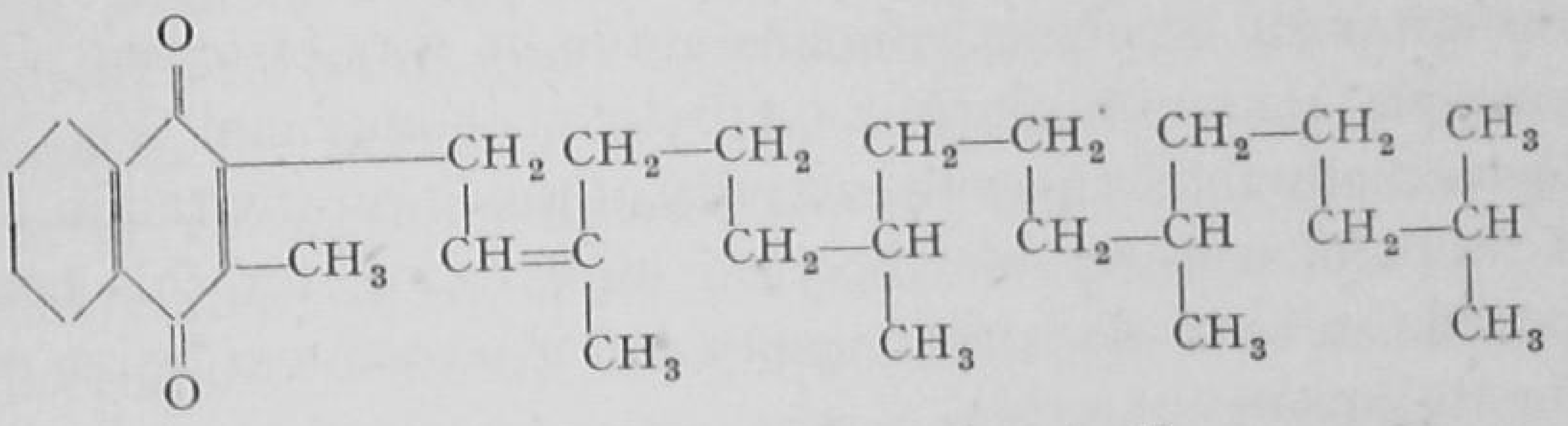


FIG. 37.—Structure of Vitamin K_1.

Thrombokinase, then, in the presence of calcium, forms thrombin from prothrombin; no clotting can take place without an adequate supply of this enzyme precursor. It is here that vitamin K comes in, for it is found that when the diet is deficient in this vitamin, the blood contains very little prothrombin. This vitamin, it would seem, is required for the manufacture of prothrombin in the liver, either as a constituent or in some accessory role.

What, then, is the nature of this vitamin K, which is so necessary if we are not to bleed to death? It turns out that there are two commonly occurring natural products which function as active agents. They are closely related to each other; both are derivatives of naphthalene, both have two oxygen atoms, and both have two side-chains, one of which is simply a methyl group and the other a long hydrocarbon chain; they are represented in Figs. 37 and 38.

These compounds are both derivatives of naphthoquinone;

it happens that many compounds of this type are easily made: the organic chemist can provide quite a number from stock. Biological examination shows vitamin K activity a property common to many of these. The special side-chains present in

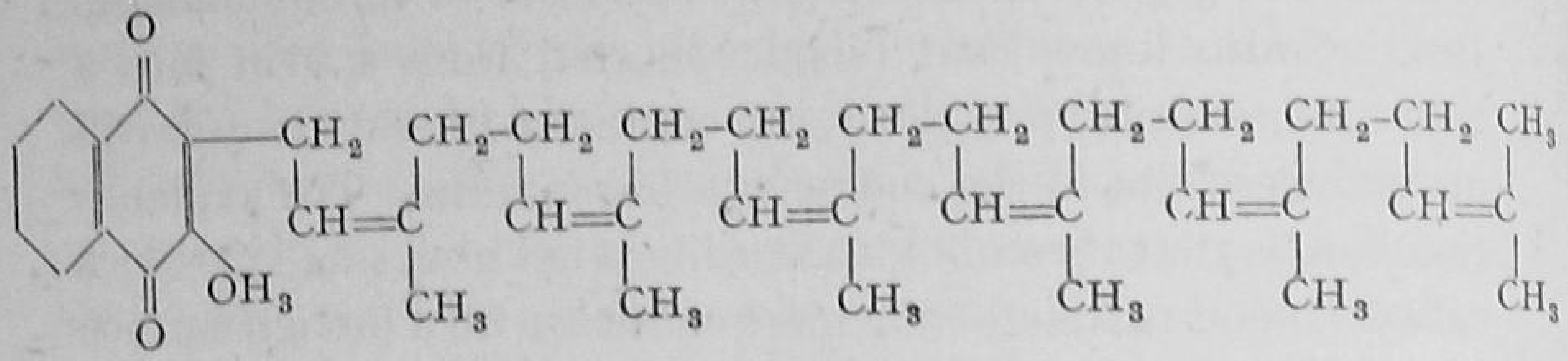


FIG. 38.—Structure of Vitamin K_2.

the naturally occurring vitamins are in no way essential. For example, the quite simple 2-methylnaphthoquinone (Fig. 39) has actually three times the activity of the natural vitamin K_1, a result of considerable practical importance, for this compound can be made fairly cheaply and is now in extensive use for therapeutic purposes.

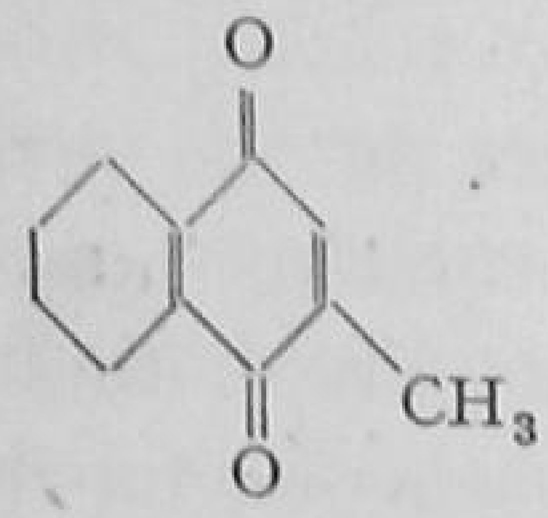


FIG. 39.—2-Methyl naphthoquinone.

The doctor does not normally find himself obliged to prescribe vitamin K because of a deficiency in the diet. This may be partly due to the fact that K is synthesized by bacteria living in the intestine so that a supply will always be available even though there is not much in the food; actually it is found in animal food such as liver, and in most green plants. It is when the flow of bile into the intestine is interfered with, as when the bile duct is obstructed by a gall-stone or an inflammatory lesion that signs of vitamin K deficiency may appear. Vitamin K is insoluble in water, but is soluble in fatty material. Now, the absorption of fats from the intestinal

tract depends on an adequate supply of bile, for this promotes the emulsification of the fatty particles into minute droplets which the gut wall is able to take up. And when the fats are absorbed, the vitamin K dissolved in them naturally is absorbed as well. But once the flow of bile is stopped, the whole process slows down, and an incidental though sometimes very important result is a deficiency of vitamin K in the system and a failure of the blood to clot properly.

It is easy to understand that this failure of the blood to clot is particularly important when the surgeon has to operate; for example, to remove the obstructing gall-stone. Fortunately it is possible by means of a suitable laboratory test on the patient's blood to find out whether the prothrombin content is up to the normal level. If it is seriously low, the patient can be given the synthetic vitamin K (methyl-naphthoquinone), along with some bile salts to promote its proper absorption (or he can be given the vitamin intravenously if necessary). In this way serious surgical bleeding due to vitamin K deficiency can be avoided.

Vitamin K has nothing to do with the rare but somewhat dramatic disease known as haemophilia. Those afflicted with this disease have blood which fails to clot, or at least clots abnormally slowly. Only males suffer from this malady, a man, as is well known, inherits his disability from his maternal grandfather, his mother conveying the disease, though not actually afflicted with it herself. The mechanism of this curious "sex-linked" inheritance is well understood; on the other hand, the precise nature of the defect in the blood-clotting system of the haemophilic is still obscure. Nevertheless, it is well established that there is no prothrombin deficiency in haemophilics, and that it is useless to give the patient vitamin K in an attempt to cure or alleviate the disease.

It is remarkable in how very many ways vitamin deficiency may manifest itself. Sometimes, as in the case of scurvy, many different organs of the body may be affected. In the

case of vitamin D, on the other hand, one particular function, namely the proper ossification of the bones, is predominantly disturbed. With practically all the vitamins deficiency is much more serious for the growing young than for adults. This is, of course, what one would expect, for in the former case it is necessary not only to make up for the losses due to wear and tear, but also to provide for the needs of the new tissues. It is only natural to expect that in the absence of adequate supplies of these components necessary for the proper functioning of body cells, growth would be inhibited. Actually, subnormal growth of the young is perhaps the commonest symptom of vitamin deficiency. But vitamins are known which have a much more specific action. For example, we may take the very interesting case of vitamin E, required by rats, and possibly by other animals during the reproductive period. In its absence both males and females are infertile. The reproductive cells of the male become atrophied; in the female conception can take place and the embryos begin to develop, but they die after a short time. A relatively rich source of vitamin E is the oil obtained from the germ of wheat seed; it is also found in rice germ and cotton-seed oils, as well as certain foodstuffs of vegetable origin. Two active compounds have been isolated, called α and β-tocopherol; both are oils, of the formulae $C_{29}H_{50}O_2$ and $C_{28}H_{48}O_2$ respectively, which yield well-defined crystalline derivatives. The synthesis of α-tocopherol has been recently achieved by the Swiss chemist Karrer, and also by Drs. Todd, Bergel, Jacobson, and Work, of the Lister Institute, London.

So far we have cited four vitamins which are fat-soluble, A, D, E, and K, and only one which is water-soluble, C. Actually, the majority of the known vitamins are water-soluble, but it is customary to classify most of the remaining ones together as the B group, and it will be necessary to devote a separate chapter to these in order to deal adequately with them.

CHAPTER XIII

THE BUSY B'S

IF you speak to a biochemist of vitamin A or C or D, he will know roughly what you mean in spite of the minor ambiguities we have had occasion to refer to in the last chapter; but if you speak of vitamin B, you will leave him guessing.

There was a time when the name "vitamin B" seemed to have a distinct meaning. A nervous disorder called beriberi develops in birds or in man if their diet consists of polished rice, and water extracts of the rice polishings or of yeast will prevent this disorder. These extracts were assumed to contain a vitamin in whose absence beriberi developed. It was later found that such extracts contained not one factor but many, and that under suitable conditions of experiment, deficiency diseases developed in appropriate animal species, which could be cured by administering the correct one from out of these numerous factors. There is indeed a whole group of accessory food factors usually found in association. They are all more soluble in water than in fat, all but one contain nitrogen, and most of them are present in the crude extract only in very low concentration. We speak now of these vitamins as forming the B group, and it has been found best to give the various members of this group special names as their characteristic biological activity was established and the pure agent obtained in a crystalline form. By now most of these have been obtained pure and have been identified with compounds already known, or, if new, have had their structures established and then been synthesized in the laboratory.

This B group of vitamins, then, contains some eight or nine well-defined compounds whose constitution is known. They form a rather heterogeneous assortment: it is only because they occur together and are extracted together from sources

such as yeast or liver that they are usually spoken of as forming a group. And yet this classification turns out to be not quite so arbitrary as it appears at first sight. Several of these factors operate in the cell metabolism in a similar kind of way. To explain just what the nature of their function is, we must first of all look at one or two of them and say something of their nature and general properties.

We have already become acquainted with one of the members of this B group of vitamins. It will be remembered that one of the "stepping-stones" over which hydrogen passed on its way to unite with oxygen (p. 117) was riboflavin. The biochemist calls this compound a co-enzyme, which just means that is it part of an enzyme system which is of relatively simple structure (as compared with a protein) and is not rapidly destroyed by heat. This functioning of one of the members of the B group as a co-enzyme is not a mere isolated occurrence; as we shall see shortly, a fair proportion of the B factors are closely related to co-enzymes. The general reason for this is fairly clear. First of all, co-enzymes are very important for cell metabolism; they are therefore essential for the health of the organism. Secondly, they are of necessity widely distributed in living tissues; it follows that they are likely to be present in animals' food, and so they are compounds the animal need not synthesize for itself. The animal organism, like the modern citizen, usually prefers to rely on getting what it wants ready-made rather than make it for itself. Hence, it is necessary that these co-enzymes, or at least their essential components, should be present in the food. This reveals the natural connexion between co-enzymes and vitamins. The co-enzymes being closely associated with soluble proteins, are themselves water-soluble, and so tend to be extracted together from sources such as yeast; and we have seen that it is precisely this chance association which has caused them to be classified together.

Riboflavine, which is essential for the proper growth of rats, is found to consist essentially of a fused system of three rings,

called an *iso*alloxazine nucleus, carrying three side-chains. Two of these are methyl groups and the third has a structure very closely related to the sugar ribose—hence the name. This vitamin, which is represented in Fig. 40, has now been prepared synthetically in the laboratory. There is in this case no evidence that other similar active compounds exist in nature, but it has been found possible to synthesize a number of

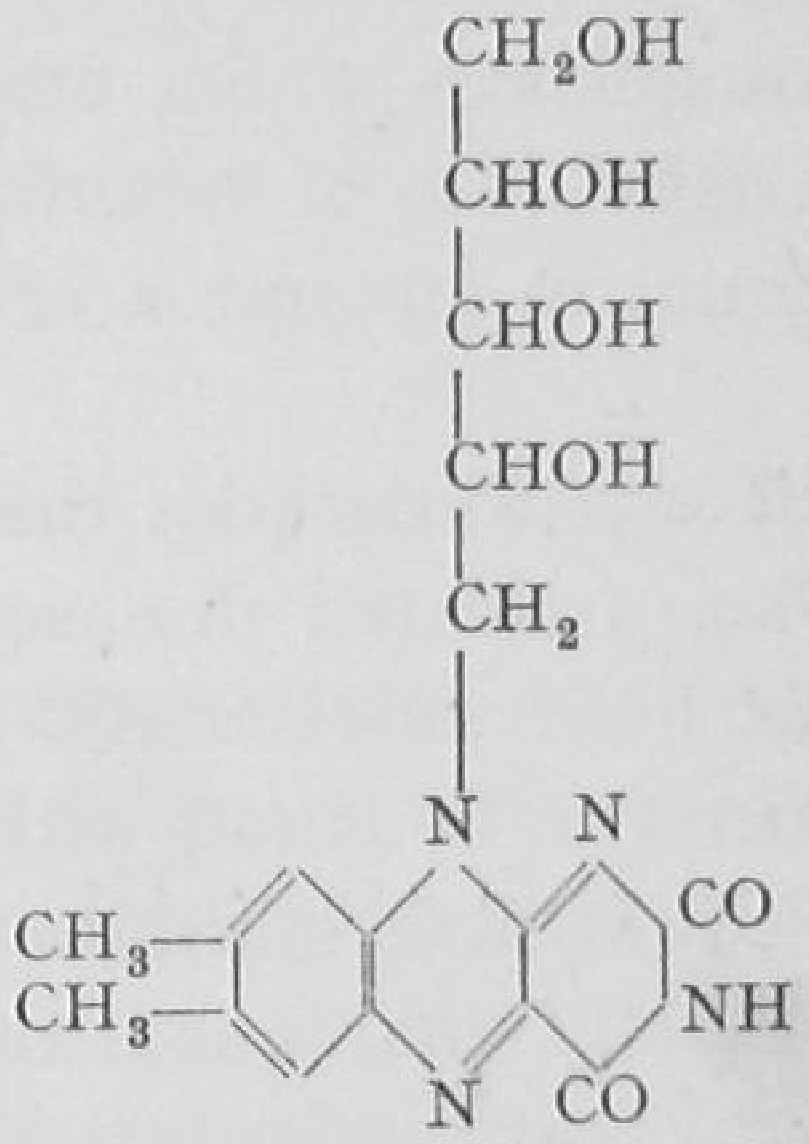


FIG. 40.—The Structure of Riboflavin.

related substances by methods similar to those employed in the synthesis of the vitamin itself. Some of these synthetic products possess definite activity, though in no case is this as great as that possessed by the naturally occurring vitamin. Thus the omission of one of the methyl groups reduces the activity to half of the original value. Omission of the ribose side-chain results in complete inactivity, but the molecule may be modified in various ways and still retain some effect. For example, if the ribose configuration is replaced by a closely related one, namely that of arabinose, the activity is reduced by about 70 per cent.

Riboflavin deficiency does not seem to be very common amongst human beings in Britain, but when it does occur it results in cuts at the corners of the mouth, vascular disturbances in the cornea, and a characteristic type of pigmentation of the skin.

If riboflavin is of more theoretical than clinical interest, vitamin B_1, nowadays usually called aneurin or thiamine, is of very great importance in both respects. People fed on a diet deficient in thiamine develop the disease known as beri-beri, in which there is a degeneration of the nerves; the heart is also affected, and indeed death frequently occurs from heart failure. One form of the malady is accompanied by a dropsical swelling of the limbs and even of the body generally. Such are the unpleasant consequences which ensue if we fail to consume the necessary daily dose of vitamin B_1, a quantity which would scarcely equal in amount a crumb of bread or a single grain of sugar.

It has been known for several decades that pigeons fed on polished rice also develop a related disease, avian beriberi, characterized by curious head movements, loss of appetite, and ultimate death, which can be cured with dramatic speed by the addition to the diet of a little marmite (autolysed yeast) or rice polishings, as well as by small quantities of many other substances. It was obvious that the birds suffered from a deficiency of some essential factor contained in these supplements.

The isolation of the vitamin defied all attempts for many years, but after various false alarms, a crystalline substance was at last obtained which was generally acknowledged to be the vitamin itself.

The compound is especially active, and probably for this reason it exists in nature in very low concentrations. Consequently it was a very laborious matter to isolate it in sufficient quantities to elucidate its constitution, but this very difficult work was successfully accomplished by Williams and his colleagues (working in the chemical laboratories of the Bell Telephone Company!), who ultimately assigned to it the formula shown in Fig. 41. The constitution has since been confirmed by synthesis. As in the cases of ascorbic acid and riboflavin, once the constitution was definitely known it was not very difficult to prepare in the laboratory a number of compounds having closely related structures, and again it was

found that physiological activity is by no means limited to the compound which occurs in nature.

With thiamine, as with riboflavin, we know now just for what purpose the factor is needed in the animal organism. This knowledge we owe largely to the work of Professor R. A. Peters and his school at Oxford. Thiamine proves to be

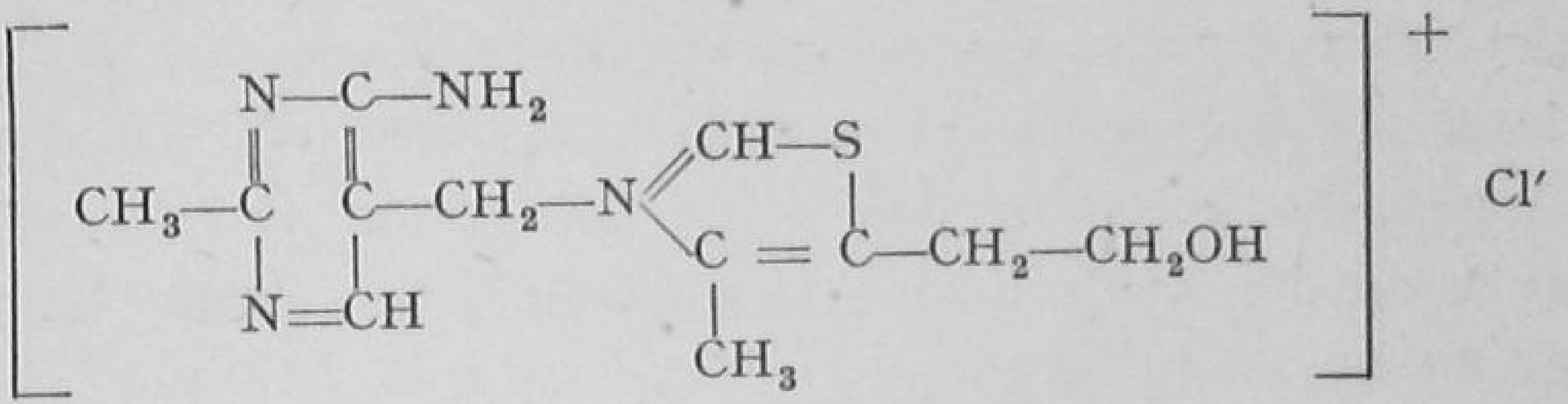


FIG. 41.—Vitamin B_1 ("Thiamine").

connected with an important co-enzyme in cell metabolism—thiamine itself, it is true, is not a co-enzyme; this role is played by a simple derivative of the vitamin, a combination of it with phosphoric acid (Fig. 42) called thiamine pyrophosphate. We have seen how glucose is broken down during muscular exercise to lactic acid. One of the intermediate products just preceding

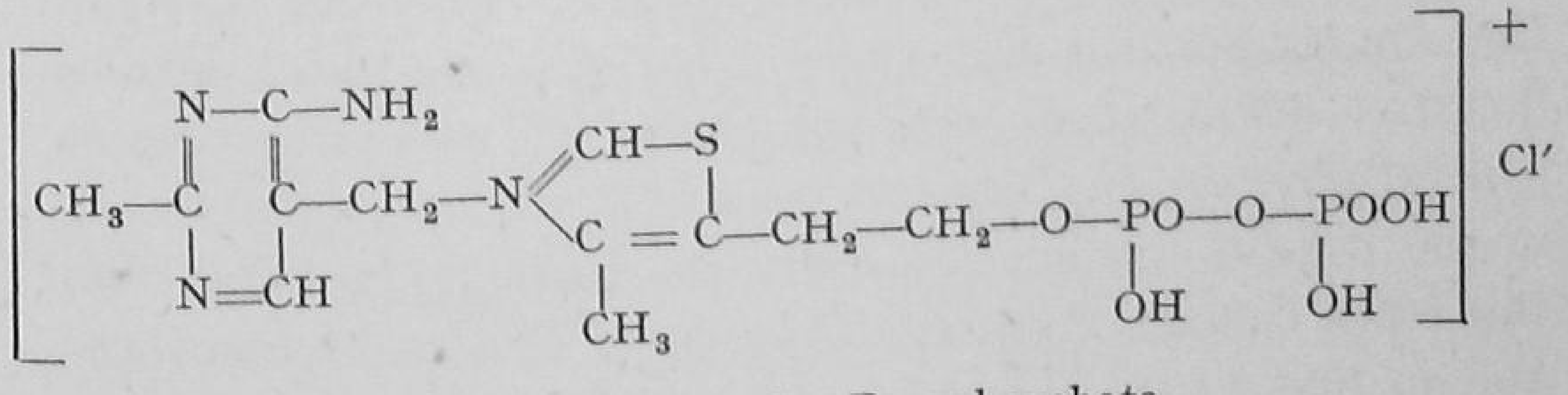


FIG. 42.—Thiamine Pyrophosphate.

lactic acid is pyruvic acid (this is also one of the stages through which glucose passes on its way to alcohol during fermentation by yeast). Now pyruvic acid, as Peters showed, cannot be properly dealt with in the cell unless thiamine pyrophosphate is present. It seems indeed that it is the failure of the tissues to metabolize pyruvic acid that is the main cause of the symptoms characteristic of beriberi. This acid is always being formed from its precursors, and when thiamine phosphate is

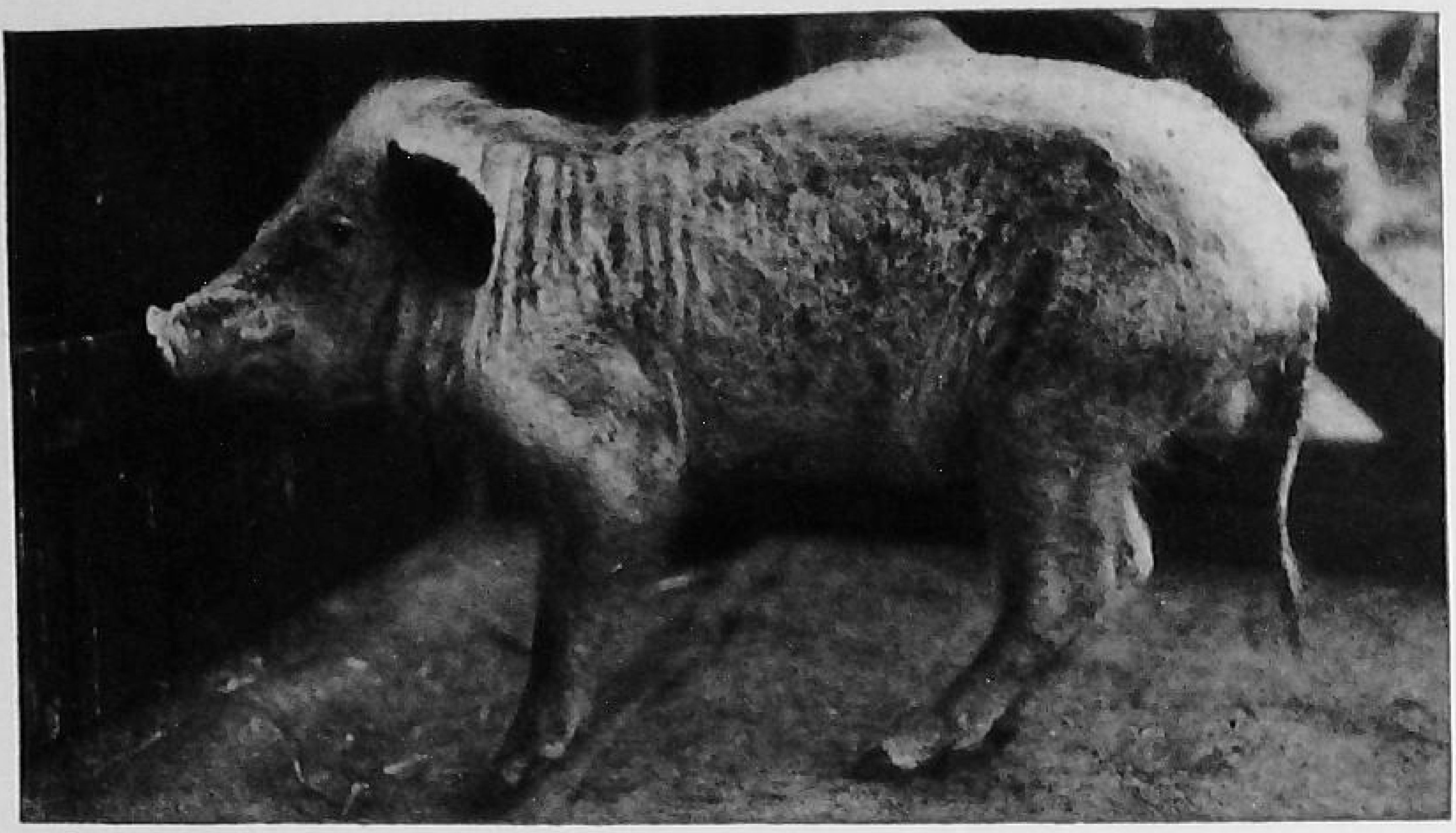
lacking, the acid accumulates in the blood tissues and, perhaps most serious of all, in the brain, and so produces nervous and other disorders.

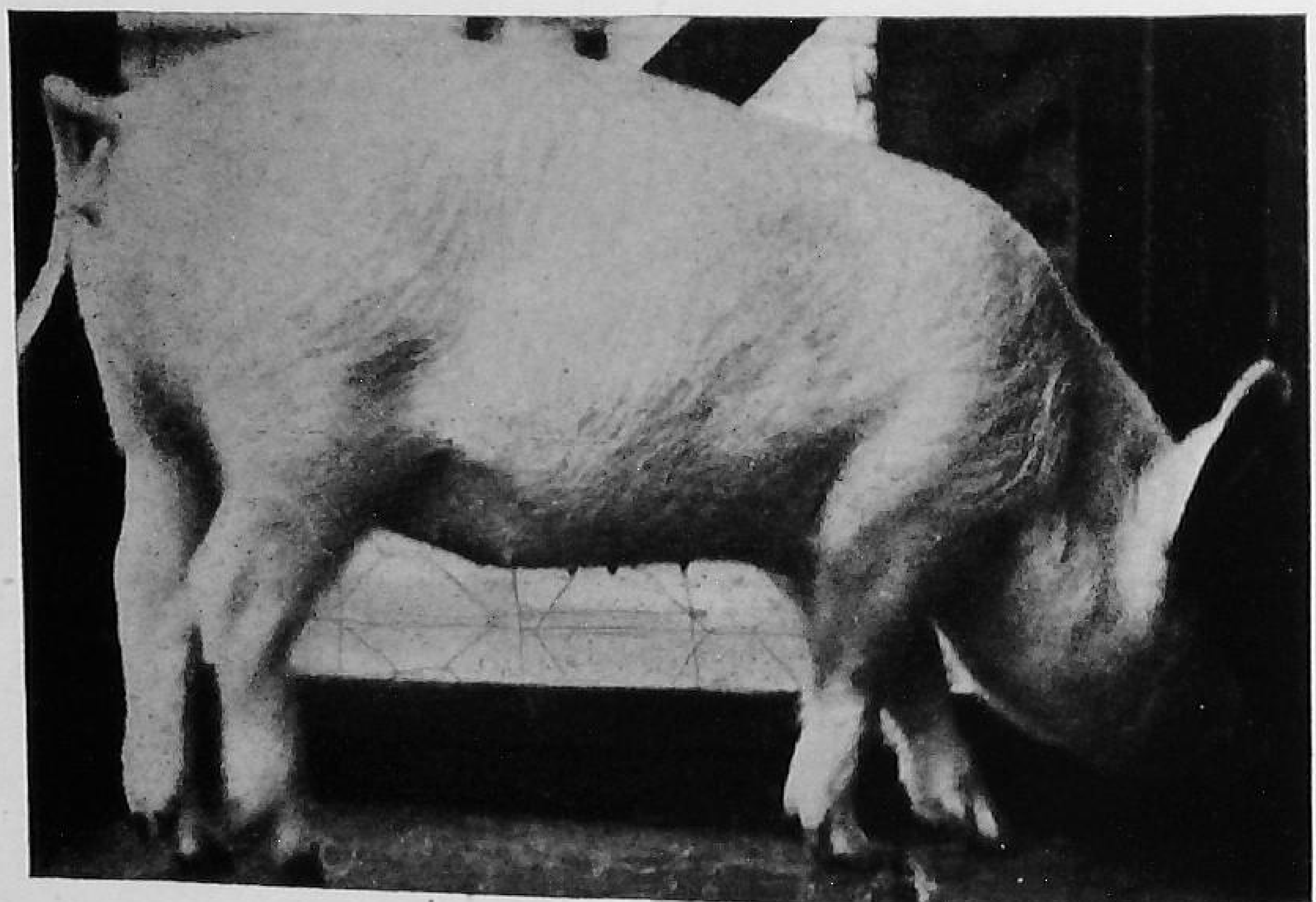
Our third vitamin of the B group is also closely connected with co-enzyme activity, though here the relation is not quite so simple as in the case of thiamine or riboflavin. The reader will remember that the two co-enzymes, co-dehydrogenase I and II, both contain as a constituent from which the molecule is built up, the pyridine derivative nicotinic acid amide. It was actually the occurrence of this compound as a structural unit in an important and widely distributed co-enzyme that suggested it might be a hitherto unrecognized vitamin. It was the kind of compound which it seemed unlikely the animal organism would be able to synthesize. The clue was followed up, and as a result a widespread and mysterious disease was explained and the way to its prevention and cure revealed.

Pellagra is a malady especially common in certain areas where the general standard of nutrition is low, and particularly where maize is the staple foodstuff, but it is not unknown even in relatively wealthy countries, such as Britain or the United States. Pellagra is characterized by a pink rash over parts of the skin (in Spain it used to be called *mal de la rosa*), serious digestive disturbances, nervous irritability, and in bad cases general physical and mental decay. During the third decade of the present century it became increasingly probable that this was a deficiency disease, like rickets, scurvy, and beriberi, and in due course it was established that a certain factor, associated with others in the water-soluble B group, was able to cure the disease. The B group was first divided into B_1, the anti-neuritic or beriberi preventing factor, which we have already discussed, and the pellagra-preventing or B_2 component, which was more resistant to heat. B_2, however, was itself soon found to be complex, and one component, riboflavin, was isolated as a definite crystalline compound necessary for the growth of rats.

Such, then, was roughly the situation when the discovery

PLATE IV.





Pig before and after treatment with nicotinic acid. The top photograph was taken at 6 months and the lower at 9 months.
(See page 211).

(By permission from Miss H. Chick, Biochem. Journ.)

was made that nicotinic acid was an essential constituent of what was obviously a very important compound in most, if not all, living cells. Could the animal body synthesize this structure? If not, then it was probable that healthy existence would be impossible unless nicotinic acid or some suitable precursor were taken in the food. Might not nicotinic acid be really a vitamin, one not yet recognized? Could it by any chance be the missing pellagra-preventing factor?

The question was soon answered, first, by experiments on animals which had developed a disease analogous to pellagra in human beings and, finally, by the direct treatment of human pellagrins. Dogs on a pellagrous diet develop a condition known as "black tongue". Elvehjem, of the American State Department of Agriculture, showed that these dogs were rapidly cured when treated with nicotinic acid or its amide. Pigs on a maize diet develop skin and digestive symptoms bearing a close similarity to those observed in cases of human pellagra, and workers at the Lister Institute, London, showed that such emaciated, almost moribund animals are rapidly restored to health by the administration of 60 mg. (1 grain) of nicotinic acid per day (see Plate IV).

Almost at the same time experiments were carried out on human pellagrins, both in America and in Egypt. It was found that doses of nicotinic acid of about 60 mg. (1 grain) per day were sufficient to dispel the characteristic symptoms of the disease. Sometimes the cure was complete, sometimes the health of the patient, though much improved, was still imperfect. It is probable that the poorness of the diet which is responsible for the nicotinic acid deficiency often results in a lack of other factors as well; but in spite of these complications, it would seem that nicotinic acid is to be regarded as the pellagra-preventing vitamin. It is interesting to reflect how much suffering would have been saved if a fraction of the nicotine destroyed in the pipes and cigarettes of the smokers of the world had been extracted and converted to nicotinic acid for the treatment of pellagra. For though the smoker

inhales no appreciable quantity of nicotinic acid, it is a simple and inexpensive process in the laboratory to convert nicotine into this important product. What is one man's poison might well be made into another's meat.

One more example remains to be given of the relation between the B vitamins and co-enzymes. Feeding experiments on rats show the existence of a food factor necessary to prevent the development of an acute dermatitis, and this factor was found along with the other B vitamins in, for example, yeast and liver. It was isolated, purified, and its structure duly

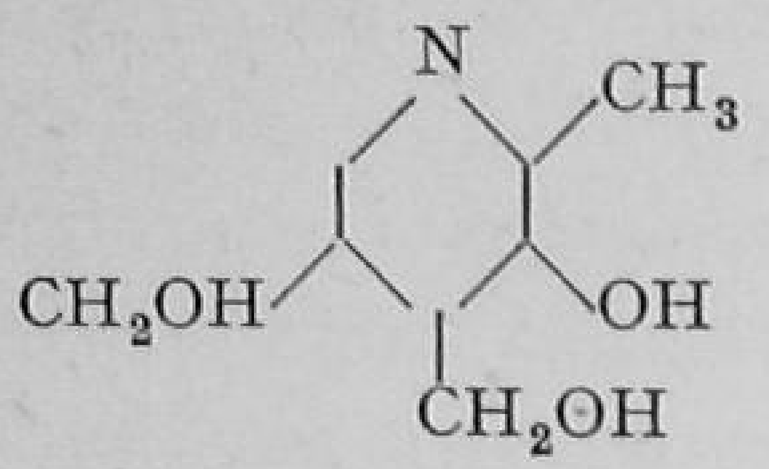
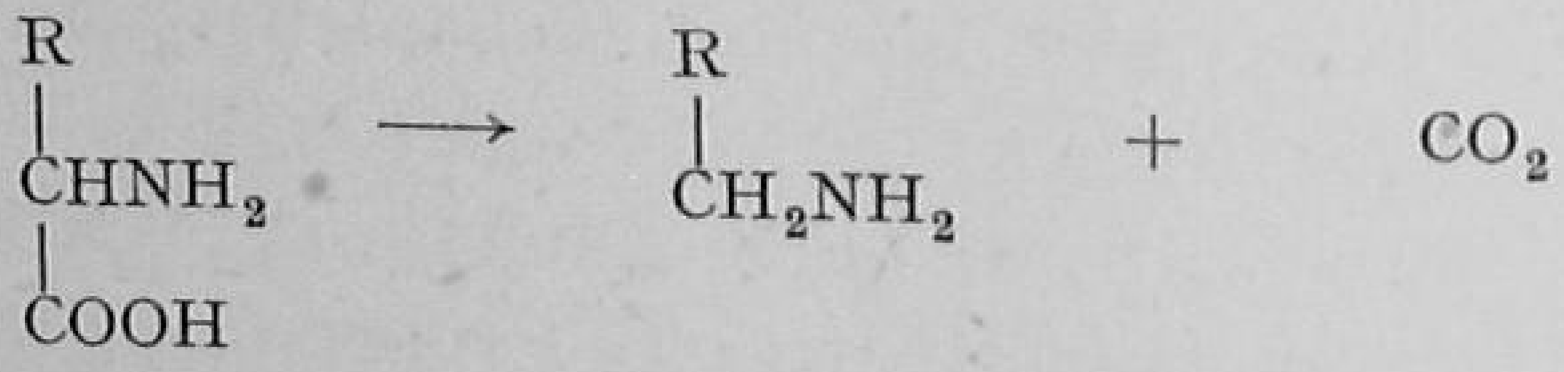


FIG. 43.—Pyridoxine.

ascertained and confirmed by synthesis. Like nicotinic acid, it is a derivative of pyridine; it iscalled pyridoxine or adermine, and is represented by Fig. 43.

And now as to its co-enzyme function. The enzyme system which is involved is one we have not so far encountered; it is concerned with the removal of the carboxyl group from an amino-acid, carbon dioxide being liberated and an amine being formed, thus:



Such enzymes are called rather cumbrously amino-acid decarboxylases, and some, though not all, require a co-enzyme. This turns out to be nothing else than a derivative of pyridoxine containing phosphoric acid. There are indications that this derivative also acts as a co-enzyme for at least one other important enzyme system; like adenylic acid, it acts as a go-between, linking together independent enzymic processes, helping to integrate them into a single co-ordinated system.

To introduce the remaining vitamins of the B group, we shall make a brief excursion into biochemical history. Yeast grows easily on a "natural" medium such as beer wort, but if we use a "synthetic" medium containing only known constituents such as glucose, ammonium salts, and so on, the matter is not quite so simple. In 1901, Wildiers, a medical student working in Professor Ides' laboratory at Louvain, published the puzzling observation that while in such a medium a relatively large inoculum started growing without much difficulty, a small inoculum of only a few cells would not grow at all. Small inocula would, in fact, grow on beer wort, or on "synthetic" media primed with a small amount of a suitable extract of, for example, boiled yeast or meat. Something was evidently present in such extracts which was necessary for the yeast growth; the unknown substance was provisionally named "bios". When a large inoculum was used, sufficient "bios" was carried in the inoculum to raise the concentration of it in the medium to the necessary level. It was also clear that once conditions were suitable for growth, yeast could itself synthesize more "bios", and so it was only at the commencement of growth that the question of "bios" entered.

But what is "bios"? It took biochemists a long time and a great deal of work to answer this question. The quantities involved are very minute; this was soon realized; and as it turned out "bios" is not a single substance. Put in another way, yeast requires for its growth the presence in the medium of several "accessory" factors, in addition to the ordinary sources of carbon and nitrogen and the inorganic salts.

One of these factors was found to have the character of an acid, and because of its presence in apparently almost all living tissues, it was called pantothenic acid. It was isolated by R. J. Williams, of thiamine fame, who also elucidated its constitution and synthesized it (Fig. 44).

As yet, we do not know what part pantothenic acid plays in the cell metabolism. It is easily broken up into an acid, called pantoic acid, and a curious amino-acid β-alanine, the

latter differing from ordinary alanine and, indeed, from all the usual amino-acids, in having the amino group further removed from the carboxyl group. β-alanine occurs in two other compounds, both present in muscle tissue, and the

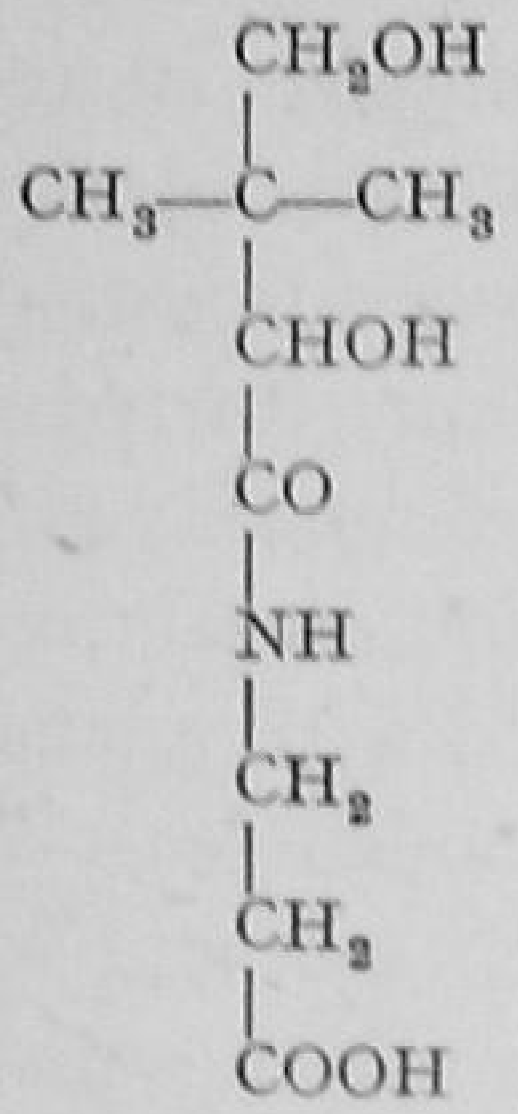


FIG. 44.—Pantothenic Acid.

explanation of its presence may give a key to some still unknown aspect of cell chemistry.

A second component of "bios" was even more elusive than pantothenic acid; it is present in exceedingly minute amount, and is relatively complicated in its structure. Thanks, however, to the brilliant work of the Dutch chemist Kögl and the Americans Du Vigneaud and Harris, and their colleagues,

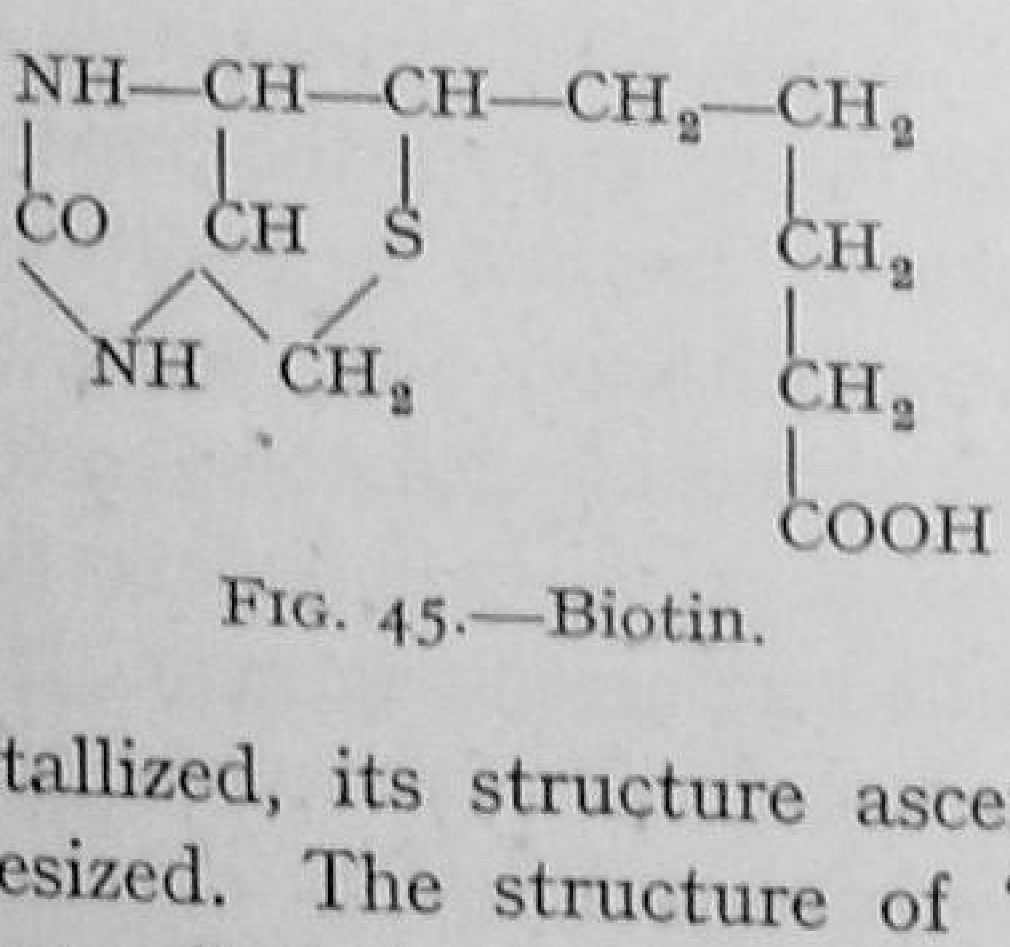


FIG. 45.—Biotin.

it has been crystallized, its structure ascertained, and the compound synthesized. The structure of "biotin", as this compound has been called, is represented in Fig. 45.

Recently a complication has arisen: Kögl has discovered that the "biotin" of egg-yolk is somewhat different from that

found in liver or milk. It is the former one, β-biotin, which has been synthesized. The structure of the other, α-biotin, is still uncertain.

Biotin, then, was discovered as a factor necessary for the growth of certain micro-organisms. It was known to be present in liver and other animal tissues; was it then a vitamin in the ordinary sense, needed for the proper growth and well-being of animals? The answer to this question turned out to be "Yes"; but this conclusion was reached only by a curious and complicated path—it was the by-product of the resolution of an apparently unrelated dietetic mystery.

In the early twenties of the century, various workers who attempted to feed laboratory rats on a diet in which dried raw egg-white provided the protein, found that their animals soon became ill, developed a dermatitis, and a characteristic paralysis of the hind-legs which caused them to adopt a kangaroo-like attitude. If the egg-white was replaced by some other protein such as casein, the animals grew and flourished. It looked as if the egg-white contained some toxic material; but this toxic factor, if such was indeed present, was evidently a rather peculiar one. Its bad effects, it seemed, could be easily neutralized by the addition of suitable supplements. By the middle thirties, a new sort of vitamin had been postulated, namely, vitamin H, defined as the factor which neutralized the toxic effects of egg-white on rats. Attempts were naturally made to concentrate and isolate vitamin H, and it was noticed that the distribution in nature and the general properties of this hypothetical substance were very similar to those of biotin, which by this time had been fairly intensively investigated. In 1940 Szent-Györgyi and his colleagues established that biotin could definitely antagonize the toxic effects of egg-white, that it was in fact identical with vitamin H. About the same time it was shown that the toxic factor was a protein present in small amounts in the egg-white. This protein has been called avidin. It has the peculiar property of forming a very stable compound with biotin which in the

stomach and intestine resists the action of the digestive juices. Biotin in this combined form passes unabsorbed through the digestive tract and is excreted. Consequently, the animals fed on a diet rich in egg-white are effectively deprived of any biotin which may be in the food, and really suffer from acute biotin deficiency.

Biotin is widely dispersed in natural foodstuffs, and is effective in very low amounts. Furthermore, it may be produced by some of the bacteria which normally inhabit the intestine. It is not to be wondered at that biotin deficiency is not met with as a common human disease, like scurvy or beriberi. Cases of human biotin deficiency are, in fact, known, but they turn up only under somewhat extraordinary conditions.

In the Georgia University Hospital, four anonymous volunteers, heroic in the service of science, started living on a diet poor in biotin and rich in egg-white. After several weeks, they became ill, exhibiting various symptoms, including a scaly dermatitis, nausea, ashen-grey pallor, and disturbances of their sense of touch. When treated with biotin their symptoms began to abate in a day or two, and had largely disappeared in a week. They were evidently suffering from a deliberately induced biotin deficiency.

But these self-sacrificing martyrs of science are not the only human beings who have suffered from biotin deficiency. A few years ago, just after the connexion between egg-white disease and biotin had been elucidated, an American labourer of Italian origin was admitted to hospital suffering from rather unusual symptoms, including a pronounced dermatitis. Investigation showed that for some obscure reason this man had unusual tastes in food. In fact, it seems, he lived almost entirely on raw eggs and alcohol. He was so fond of eggs that he ate up to six dozen a week, and had deserted his family in order to start a chicken farm. It was an easy guess that he might be suffering from biotin deficiency; the avidin in the egg-white would neutralize the biotin in the yolk. He was

treated liberally with biotin; his symptoms rapidly abated. Whether he gave up his passion for raw eggs does not seem to have been recorded.

To avoid a possible misunderstanding, we should perhaps emphasize that yeasts are not the only micro-organisms which require to be supplied with factors such as pantothenic acid and biotin for growth. Many other micro-organisms, such as certain bacteria, are even more dependent on external sources of such compounds; yeasts seem to be able to synthesize them once they are present in sufficient amount to enable the cell metabolism to work satisfactorily; but these bacteria seem unable to do this, and like many of the higher animals, are completely dependent on external sources of supply. There is very great variation from species to species and even different strains of the same species may not possess identical synthetic powers. Indeed, yeast affords an example of this fact, for some strains are less dependent on certain factors than are others, and in the early days of the "bios" problem a good deal of controversy took place, based on inconsistent experimental findings, probably a consequence of this subtle biological variation. Since sundry strains of bacteria and other micro-organisms require one or more of these factors to ensure multiplication, we must replace the idea of a yeast "bios" by the more general conception of "accessory growth factors" for micro-organisms. Besides the original "bios" factors, we have to include the other members of the B group originally encountered as vitamins necessary for mammals, riboflavin, thiamine, nicotinic acid, and pyridoxine. This dependence of the growth of micro-organisms on specific compounds of this group has afforded a method for the detection and estimation of any one of them. The general principle is to provide a medium which is completely adequate for growth in every factor except the one in question, and then to examine the effect of the addition of known quantities of the hypothetical source of this factor. The growth response is compared with that given by a standard preparation. The idea is the same

as that used in the assay of vitamins by measuring the effect on the growth of, say, rats or mice on a defective diet, but it has the advantage of being quicker and of requiring much lower amounts for a satisfactory assay. Some of these "accessory growth factors" are indeed effective in amazingly

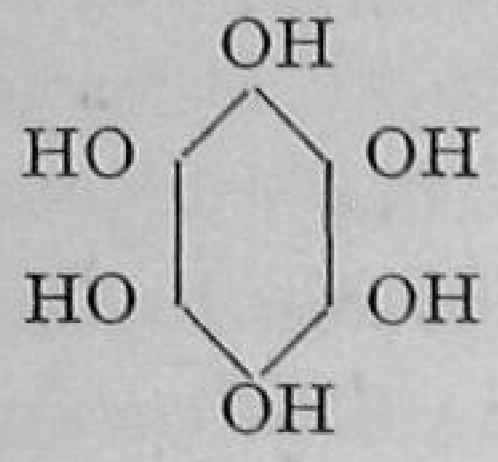


FIG. 46.—Inositol.

small doses and, as one might consequently expect, are present in nature in very low concentrations. Biotin, for example, promotes the growth of micro-organisms when the medium contains concentrations of as little as 1 in 10^{10}; Kögl obtained 1·1 mg. of this compound from a quarter of a ton of egg-yolk.

Amongst the accessory growth factors not yet mentioned are inositol, uracil, and *p*-aminobenzoic acid; all compounds well known to the organic chemist long before the days of vitamins and "bios", but not suspected of having special significance in metabolism. Inositol (Fig. 46) resembles

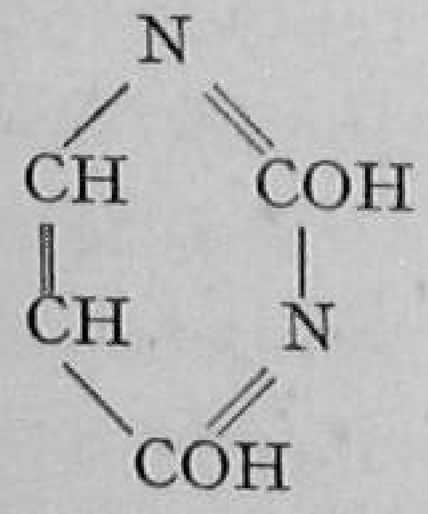


FIG. 47.—Uracil.

glucose in containing six carbon atoms and several hydroxyl groups, but it is less chemically active and though its widespread distribution clearly suggests it has some important function in metabolism, its rather inert nature makes it difficult to guess what that function can be. It differs from the other factors of this group in being free of nitrogen. Uracil contains a ring system present in thiamine and in riboflavin

(Fig. 47). Though the wide biological importance of this "pyrimidine" ring has in recent years been generally realized, we still lack a significant pointer to its actual function.

The last factor we shall refer to is *p*-aminobenzoic acid, and the indirect route which led to the recognition of the importance of this compound in bacterial metabolism is another illuminating example of the almost adventitious way in which science sometimes advances. Nowadays everybody is familiar with the "sulphonamides" and their great clinical importance in the treatment of certain bacterial diseases. It

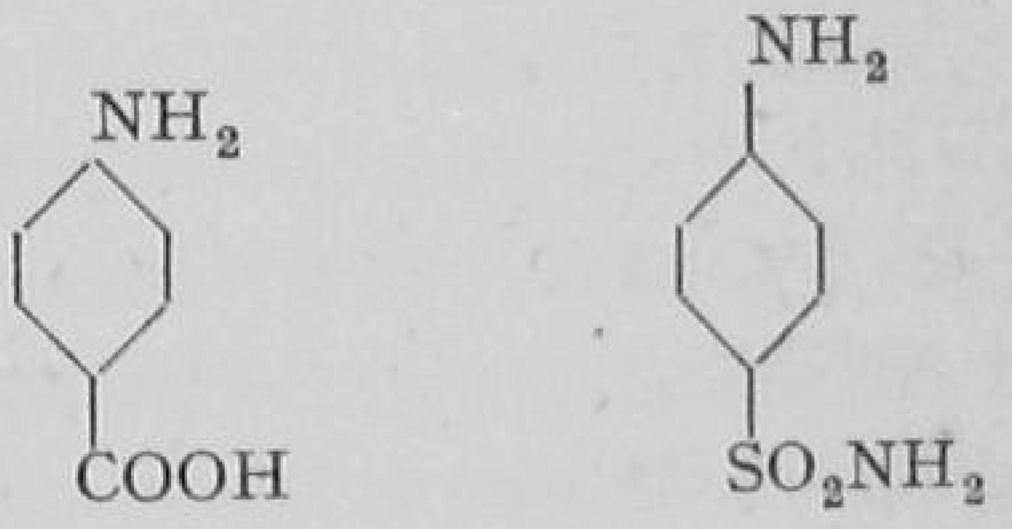


FIG. 48.—*p*-Aminobenzoic acid and sulphanilamide.

was in 1935 that the world first heard of "prontosil", a dyestuff which a German bacteriologist, Domagk, had found to be able to cure mice suffering from certain bacterial infections. The peculiarity of this dyestuff was that it contained a "sulphonamide" group (—SO_2NH_2), and within a year or so the French workers, Nitti and Bovet, had shown that the important part of the molecule was this group and the atoms to which it was immediately attached; that, in fact, *p*-aminobenzene sulphonamide or sulphanilamide (Fig. 48), which was formed from the dye in the animal organism, was apparently the curative agent, and that this simple compound was just as effective as the dye itself. *p*-Aminobenzene sulphonamide had been made in the laboratory by Gelmo many years before (1908), but its remarkable virtue as a drug had remained unsuspected all these years. And now the question arose, how did sulphanilamide work?

The clue to the answer was given by following up an apparently secondary observation. This was that it was much

less active in inhibiting bacterial growth—for sulphanilamide turned out to be an inhibitor of bacterial growth rather than an agent lethal to the organisms—when extracts of certain tissues, or of yeast, were present along with the drug in the medium in which the bacteria were inoculated. D. D. Woods investigated the nature of the substance antagonistic to sulphanilamide in yeast extracts, and though he did not actually isolate the compound, he produced evidence very strongly suggesting that it was *p*-aminobenzoic acid. A sample of this compound prepared synthetically Woods showed to possess the inhibiting action; and soon afterwards Rubbo and Gillespie, in Australia, completed the proof by isolating *p*-aminobenzoic acid from yeast. A little earlier, a general theory had been advanced by Professor Fildes to explain antiseptic and chemotherapeutic action; that is, the toxic effect of certain chemical agents on bacteria and other micro-organisms. We may call it the theory of the jammed cogwheel. If we want to put a machine out of action, there are several methods we may adopt. We may use the time-honoured device of dropping a spanner into the works. But this is a somewhat crude and inelegant proceeding. A more refined and discriminating method of sabotage is to select some really important cogwheel, and deliberately and effectively to jam this. In chemotherapy, the problem is to knock the mechanism of the invading micro-organisms out of action, but to leave that of the body-cells intact. If we merely tried to drop a spanner in the works, it might just as easily drop into the works of the host's cells as into those of the disease germs. But if we concentrate on jamming a cogwheel, we have a greater chance of causing the trouble just where we want it, for we can select a kind of cogwheel which, though important in the parasite, is not really material to the proper functioning of the host, or even better, may not exist in his cells at all.

The actual jamming could be done in various ways. We might perhaps twist one of the teeth so that it no longer fitted; we might replace the cog by a complete misfit, an oversized

one; we might even remove the cogwheel altogether. Fildes' general theory does not prescribe any particular method of jamming the cogwheel, but among the various possibilities is one which corresponds closely to twisting one of the teeth so that it no longer fits. But let us interpret the idea in more chemical language. Fildes' idea is that the mode of action of many at least of our antiseptic and chemotherapeutic agents is by interfering with an "essential metabolite". An "essential metabolite" is some substance which plays an essential part in the processes of the cell metabolism: it is a cogwheel in our machine. What about the cogwheel with the misfitting tooth? The chemist can provide this by treating the organism with a compound like the essential metabolite, but differing to some extent. It has to be sufficiently like the metabolite to take its place in the mechanism of cell metabolism, but sufficiently unlike it to jam when the chemical wheels begin to turn.

In the application to the sulphanilamide problem, the idea is that *p*-aminobenzoic acid is an essential metabolite, an important cogwheel in the bacterial cell, and that sulphanilamide which is just the same with —COOH replaced by —SO_2NH_2, is the same wheel, but with a twisted tooth (Fig. 48). The idea is that the resemblance is sufficiently close to allow the sulphanilamide, when present in high enough concentration largely to displace the *p*-aminobenzoic acid, so preventing it from taking part in its normal reactions; but having done this, it jams the mechanism, being unable to copy the behaviour of the *p*-aminobenzoic acid completely.

It might be thought that this theory of the mode of action of sulphanilamide, based on a general and perhaps somewhat superficial resemblance, is rather far-fetched, but there is a good deal of evidence, some of a rather striking character, which supports the idea. The vitamins of the B group may be regarded as essential metabolites for at least some micro-organisms, Now, on the basis of the idea of interference by similar substances, it has been found possible deliberately to modify the structure of many of these factors in such a way

that they actually inhibit growth instead of promoting it. Here are two or three examples which show what can be done. A compound resembling nicotinic acid amide (Fig. 49) is pyridine-3-sulphonic acid (Fig. 50). It is found that this latter compound inhibits the growth *in vitro* of staphylococci which require nicotinic acid amide for their growth. The inhibiting

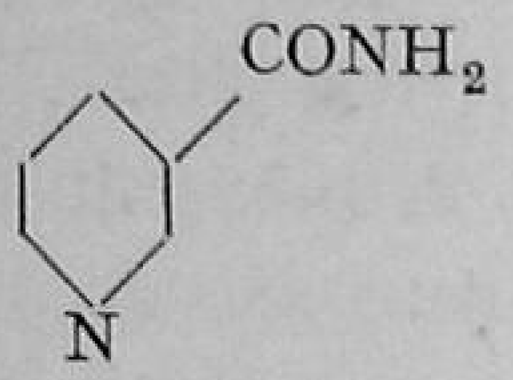


FIG. 49.—Nicotinic acid amide.

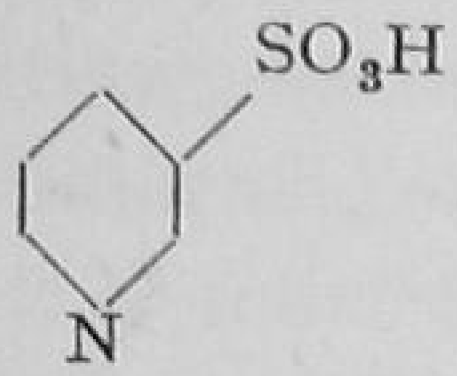


FIG. 50.—Pyridine 3-sulphonic acid.

action of the sulphonic acid is prevented by supplying sufficient of the nicotinic acid amide, just as the action of sulphanilamide is antagonized by *p*-aminobenzoic acid. Naturally, the more of the proper metabolite there is at hand, the less will be the power of the foreign compound to interfere. A second example is the very similar growth retarding effect of pantoyl-taurine (Fig. 51) on bacteria which require pantothenic acid for growth.

$$HO—CH_2—\overset{\displaystyle CH_3}{\underset{\displaystyle CH_3}{\overset{|}{\underset{|}{C}}}}—CHOH—CO.NH—CH_2—CH_2—SO_3H$$

FIG. 51.—Pantoyl Taurine.

Pantoyl-taurine is just pantothenic acid with the carboxyl group replaced by the rather similar sulphonic acid group. Here the action is not limited to *in vitro* conditions, for rats, infected with virulent streptococci, were protected by dosing with pantoyl-taurine, while untreated control animals died.

Thiamine presents a further example of how a growth factor may be modified to obtain an antagonist; here one of the rings has been somewhat altered by the substitution of CH : CH for the S atom. The new compound is definitely inhibitory to many bacteria, and in mammals it produced symptoms of

thiamine deficiency. Evidently, this pseudo-thiamine prevented the thiamine cogwheels in the organism from working properly. Its effects are, in fact, neutralized by giving thiamine itself. And, finally, consider the compound got by replacing the two methyl groups of riboflavin (Fig. 40) by chlorine atoms. This turns out, as one might expect, to be a riboflavin antagonist. Now the reader may recall that certain compounds related to riboflavin, such as arabino-flavine, so far from antagonizing the vitamin, had a vitamin-like action. It seems to be a question of the degree and nature of the modification. If the difference is small enough, the modified substance may be able to take the place of the proper factor and behave sufficiently like it to allow the cell mechanism to proceed; but if the alteration is a more drastic one, the new compound, if supplied in sufficient amount, jams the mechanism.

One of the objects of preparing these antagonists to the essential growth factors of bacteria has been to obtain new chemotherapeutic agents. *p*-Aminobenzoic acid, it is now realized, is just one of these factors of the B group; it is necessary for the growth of many organisms; and sulphanilamide is a modified factor which acts as an antagonist. Sulphanilamide was stumbled on by accident: why should not other valuable drugs be obtained by the deliberate modification of other factors? Bacterial antagonists, as we have seen, have in fact been produced in this way; but not so far any useful chemotherapeutic agents. The reason for the failure is perhaps that most of the factors are too widespread; they are important not only to the attacking micro-organisms, but to the infected animal as well. The modified factors used as drugs would probably poison the patient along with the bacteria. *p*-Aminobenzoic acid appears to have the peculiarity that some bacteria are very dependent on it, but its role in the metabolism of the higher animals does not seem to be a very vital one. Consequently, the sulphonamides are almost harmless to the patient; at the same time they act effectively against the

streptococci or pneumococci which are attacking him. The nearest to success that has been achieved so far by this new approach to chemotherapy is with the pantoyl-taurine which saved infected rats. But so far it has not proved a useful drug for human beings.

The reader may be wondering why only the B vitamins should be specially required by micro-organisms. The reason is that, broadly speaking, the B factors are concerned with such elementary processes as oxidation, decarboxylation, and reduction common to all living things. They are not concerned with somewhat specialized functions of the higher organism, like vitamin D (bone formation), E (reproduction), or K (blood-clotting). The latter vitamins have no significance for micro-organisms; they are much more specialized than the B factors.

The subject of the vitamins has grown to enormous proportions. Every month dozens of new papers appear dealing with one or other of these factors. A complete detailed account of our present knowledge of the subject would occupy a book of several volumes, and of course all this research has cost a great deal of money. What are the practical results? These are not far to seek. Rickets has been, or might be, completely abolished. The cause of scurvy is understood and the disease easily prevented. It is only the dietetic and economic absurdities of mankind that permit the continued existence of beriberi and pellagra (see p. 211). These great scourges are now understood, and here understanding should mean mastery.

But there has been another result which though less direct and less dramatic is perhaps of even greater importance for the average citizen of the Western world. The public have become "diet-conscious". They are, of course, ignorant of most of the details of the new knowledge, but a general impression has filtered through. And it is here that the invention of the word "vitamin" has been really justified. It has provided the public with an easily remembered label for a very important idea—the idea that the value of a diet does nor reside solely in its quantity or even in the nature of its major

constituents, but in part depends on the presence of other important factors, strange perhaps in their nature, but essential for healthy existence. And it has also become generally realized that these factors are particularly rich in certain kinds of food, especially fruit and fresh vegetables. All this has gone to awaken the public to the need for an adequate and varied diet, and, above all things, an adequate and varied diet for the young.

This double effect of knowledge on the community—partly direct, partly indirect—is not peculiar to vitamin research; it is a feature of medical research in general. Thus, though the knowledge of bacteriology and of the aetiology of infective diseases has undoubtedly resulted directly in the control or abolition of many serious maladies, yet quite apart from this, the public has gradually realized that dirt and insanitary conditions do constitute a menace to public health. They have in consequence become more willing to pay the price for cleanliness and common decency. They have become "sanitary minded". In a community in which active research work on medical subjects is constantly going on, interest in the problems of health diffuses in ever-widening circles until finally the whole community is willing to take practical action.

The experience of Britain during the Second World War revealed what could be done even under the most adverse conditions. Most foodstuffs were in short supply; but a carefully planned rationing scheme was introduced which ensured that everyone should get his fair share of what was going in calories, proteins, and vitamins. Enlightened propaganda taught the public to make the best of what they bought; for example, to eat green vegetables raw or to cook them in such a way as not to destroy the vitamin C. Many of us objected to the colour or perhaps to the texture of the bread made from 90 to 95 per cent extraction flour; but we realized that this dark loaf ensured us a sufficient supply of vitamin B_1 just at a time when our intake of this factor might have been dangerously low in consequence of the small meat ration. Milk

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has begun to be valued at something nearer its true worth. It is an unsurpassed source of proteins and vitamins, and the terrible extravagance of converting it into pig-food and even ladies' combs—not uncommon practices in pre-war Britain—is now universally realized. A healthier and fitter nation is all the cry: exercise and sports can do something towards this; preventive medicine can also do something; but proper diet can do more than either.

In one respect, perhaps, the vitamins are symbolic of a great change which had been going on during the last few centuries and is still proceeding. In early times the soil and the animals which fed on it were the immediate sources of practically all that man required. Gradually processes of manufacture sprang up, first no doubt the cooking and preparation of food, then the spinning of wool and weaving of cloth, and later more complex operations. Gradually we have been separated further and further from the soil, and have become dependent to an ever-increasing extent on processes of manufacture. The chemistry of nature is being supplemented, and even replaced, by the chemistry of man. So far, however, our foodstuffs are still essentially the product of the plants and the animals. No doubt it will be a long time yet before our factories turn out juicy roasts from coal-dust, water, and air. Synthetic food *en masse* is as yet afar off. But a beginning was made in that direction when a little over thirty years ago the fixation of atmospheric nitrogen became a commercial possibility. Previously the plants had to be fed with nitrogenous compounds, for the most part in the form of manure derived from animal excrement, or else were dependent on the synthetic activities of bacteria. But the solution of the problem of the technical fixation of atmospheric nitrogen made possible the replacement of these sources by artificial manures. And so the roast beef of Old England is not quite what it was: the nitrogen in it now comes not from the farmyard but from the factory.

Another change tending in the same direction is even now

in progress. Only a few years ago we were absolutely dependent for our vitamins on natural sources. Indeed, most of us believed that the nearer we kept to nature the better. Even cooking was found to be deleterious, tending to destroy these essential factors. But with the development of methods for the synthesis of certain vitamins, their commercial manufacture has become a practical proposition. Already vitamin D (calciferol), prepared by irradiation of ergosterol, synthetic vitamin C (ascorbic acid), thiamine, and riboflavine are on the market. It is true that in the first two cases natural products are utilized as starting-out materials and that the synthesis is only a partial one, but some at least of the work of the living cell has been taken over by the factory. That the manufacture of vitamins is really an important proposition is evident from the liberality with which the great chemical manufacturing companies are subsidizing research on the subject and hastening to take out patents to cover the new discoveries. However, looked at in proper perspective, these remarkable developments in the synthesis of the vitamins represent but one more stage in the great process of replacing the synthetic activities of the living cell by the synthetic activities of man himself.

CHAPTER XIV

SEX AND REPRODUCTION

IN the higher animals the pattern of life is influenced at almost every point by the fact that each species consists of two types of individual, male and female. This is in general no less true of the simpler animals and the plants—at least when allowance is made for their more elementary patterns of life. It is only in some very primitive or degenerate forms of living matter, such as the bacteria, that differentiation into sexes appears to be absent altogether. Sex is something very deep-seated in the nature of life—not, indeed, absolutely indispensable, but apparently necessary for any advance in the biological scale beyond the very simplest types.

We may be quite sure that any biological character so widespread as this differentiation into two sexes must be of supreme value to the living organism. What, then, is its biological value? Why are there two sexes, not three or four? It is, of course, no answer to say that two sexes are necessary for reproduction. Bacteria can multiply perfectly well asexually. Higher animals, such as frogs, can sometimes be made to develop from an unfertilized egg, showing that even in their case reproduction is not absolutely dependent on the co-operation of the two sexes. The device of separating all the individuals of any species into two types, male and female, and making reproduction depend on the co-operation of one individual from each type, must possess some supreme biological value. In what does this value consist? Let us, first of all, inquire what is the essential feature of sexual reproduction.

On consideration this is seen to consist in every new individual of a species being formed as the result of the union or fusion of two cells, one of each sex. The essential point is that the new individual receives his inheritance from two

parents and not from one alone; though this may appear a trivial change, its consequences for biological history have been all-important. To understand how this comes about it is necessary to consider briefly the mechanism whereby evolution is effected.

It is now generally agreed that two factors are needed for the evolution of a species: first the occurrence of variations among the individuals of the species, and, secondly, the action of selection in encouraging one type of variant rather than another. The mechanism producing these variations need not concern us here; it is sufficient to remember that they occur spontaneously, or at least as the result of causes outside the control of the organism, and that if they are to possess evolutionary value they must be inheritable. The chance of any particular variation occurring is very small as far as any one individual is concerned.

Now consider the case of the unisexual animal, in which every new individual receives his inheritance from one parent alone. In a sense he is no new individual at all, he is just a chip off the old block and is likely to possess precisely the same abilities and potentialities as his parent, neither more nor less. Nevertheless, variations will occasionally appear, so let us suppose that among the numerous individuals of the same generation two abnormal ones are found, each bearing its own unique and novel variation. Of course, if these variations are disadvantageous to their possessors they will doubtless disappear in the course of a few generations in consequence of the selection of the fittest. If, however, they are beneficial, a larger and larger proportion of the species will gradually come to be descended from these two individuals and the species will ultimately be descended from them alone. It will then consist of two distinct types of individuals, and continued competition and selection may ultimately result in the survival of only the better of the two, with the complete loss of the other variation even although it was in itself an advantageous one. There is evidently no chance of obtaining a type possessing

both advantageous variations except as the result of one of the variations occurring again, and this time in an individual already possessing the other. As the occurrence of any particular variation is likely to be very rare and indeed might never be repeated, it is evident that evolution under these conditions is likely to be very slow. Sub-types within the species might be expected—bacteria show this feature very prominently—but even in species with a very short generation-time real progressive evolution would be a very tardy process. With a longer generation-time the rate would be proportionately lower.

When there is sexual reproduction, so that each new individual receives his inheritance from two parents and not from one alone, the situation is very different. If, as before, we begin with two independent beneficial variations, it is evident that sooner or later mating will occur between two individuals each bearing one of these modifications. Consequently a certain proportion at least of their offspring will carry both, and so presumably have a double advantage in the struggle for existence. It follows that the race will tend more and more to be descended from these fortunate individuals, and will ultimately consist of them alone. The two variations no longer compete, they are readily united in one and the same individual. It is no longer necessary to wait until one of the variations recurs in the strain bearing the other.

It is evident that the argument holds with even greater cogency if we consider not two but many distinct variations. In the case of the sexual organism each of these may occur in any individual, and the possibility at once arises that an individual may ultimately appear, bearing them all. They can be combined and recombined, and the best combination which ultimately appears is likely to become increasingly predominant in the species. On the other hand, the occurrence of such an individual in the unisexual species would only be possible as the result of many unlikely events—the individual variations—all occurring either simultaneously in the same

individual or successively in individuals in the same line of descent.

Clearly the device of sex has the great biological advantage of permitting the mixing up of individual inheritances: it enables independent variations to be combined in one and the same individual. In the case of multi-cellular animals, where each produces a large number of germ cells, it is clear that the purpose of sexual reproduction can be most efficiently attained by arranging that each animal produces cells of only one type unable to fuse one with another; or if two types are produced by the same animal, then it must be arranged that fusion will not occur except with cells from another individual. In other words, the individuals will either be divided into two kinds or sexes, or else, when the individuals are hermaphrodites, as in the case of most plants and certain animals, special precautions will be adopted to ensure cross-fertilization.

We are now in a position to answer our second question: namely, why there should be only two sexes and not three or even more. Obviously two only are required to bring about the essential result. To have more would be an unnecessary complication. On the principle of *entia non sunt multiplicanda* it would be very surprising to find three sexes where two would do as well. It is true that what are virtually three sexes are found in certain species, such as bees, where the workers are specially modified infertile females, but this is clearly a special adaptation for social or economic ends and does not directly affect reproduction and inheritance. Reproduction with three sexes would indeed be a complicated and elaborate matter. Even as it is, ordinary bisexual reproduction in the higher animals has involved great specialization and very detailed adaptation, more especially on the part of the female.

It is of great interest to examine how the organism accomplishes the co-ordination of the different organs involved in the complicated process of reproduction, and how their functions are regulated and harmonized with each other. This is a

special case of the general problem which confronts the multicellular organism, that of controlling and co-ordinating its various parts so that the animal as a whole will function properly. Clearly methods of communication are necessary between one group of cells and another. The problem is analogous to that which arises in a human community with the development of civilization and the emergence of an organized state. In a very primitive society communication by touch, sight, and hearing suffice for the small amount of co-ordination required. In order, however, that the effective unit should become bigger than the family or the village, it is necessary to develop means of communicating at a distance. For this purpose the practice is established of sending communications, either oral or written, by messenger. Ultimately this develops into an organized postal service, and until comparatively recent times the smooth and harmonious working of the complex modern state was essentially effected by messages sent from one place to another in this way. But such bodily transportation takes time, and so it is now supplemented by a much faster form of communication, the electric telephone or telegraph; the larger and more widely scattered the community the greater is the advantage of these new devices.

In the animal body there is the same duplication of the means of communication. The analogy of the nerves to telephone wires, and of the nerve centres, especially of the brain, to telephone exchanges is at once obvious. But what corresponds to the form of communication by messengers? It is only during the last few decades that the answer to this question has become clear, but already a whole new subject has grown up, and the knowledge acquired is of pre-eminent importance not only theoretically, but also for the treatment and prevention of disease.

The study of these chemical messengers, or hormones as they are now usually called, began towards the end of the nineteenth century. One of the most spectacular demonstrations

of their potent effect was that given by Professor Edward Sharpey-Schafer and Dr. Oliver at a meeting of the Physiological Society in March 1894.

It is common knowledge that injuries involving extensive tissue damage produce a state of prostration and shock associated with a serious fall in the blood pressure. These effects can also be produced, as might be expected, by injecting into the blood-stream extracts of practically any minced-up

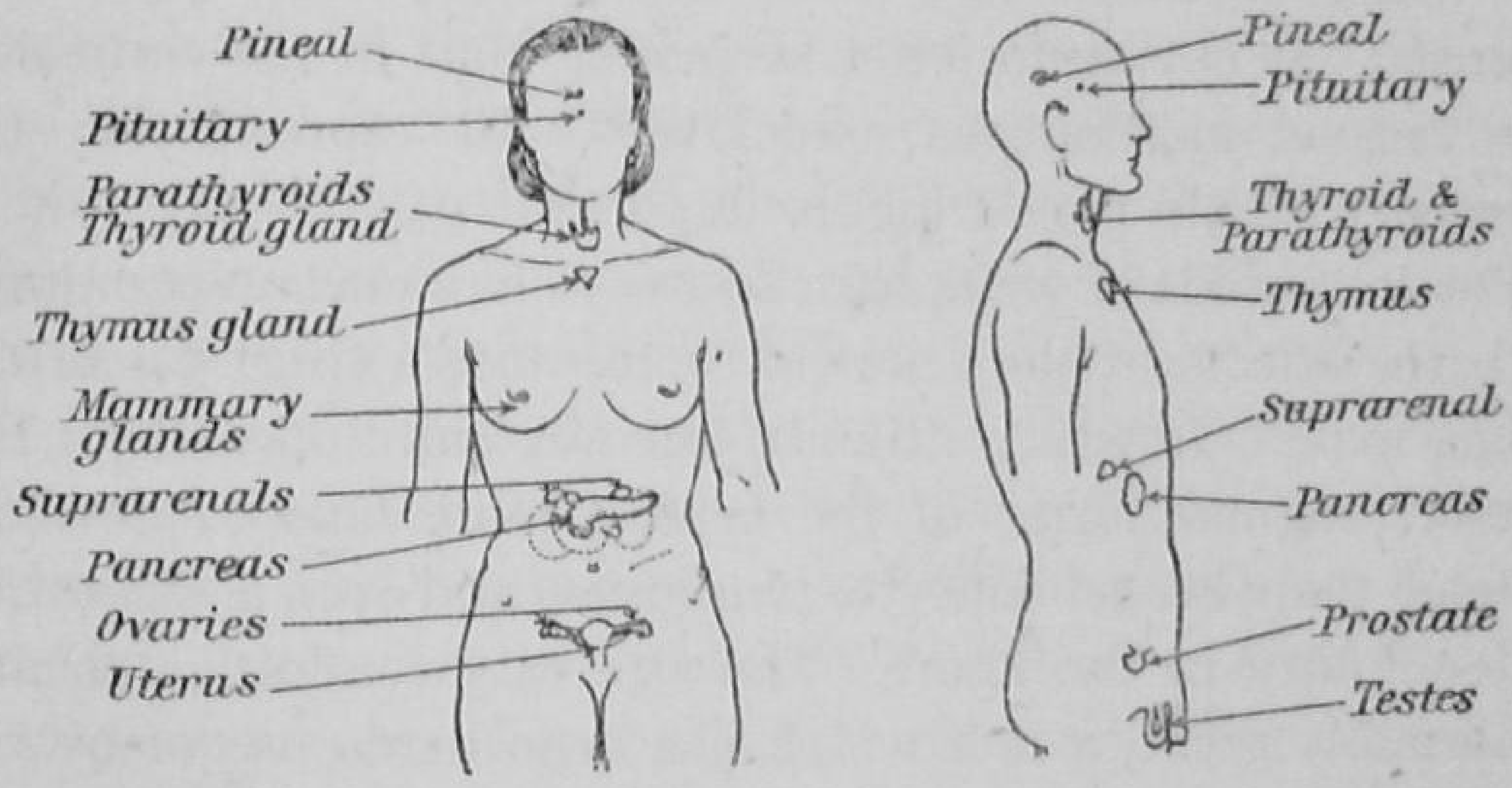


FIG. 52.—Illustrating the position of the endocrine glands of the human body.

tissue. Imagine, therefore, the surprise of the audience when the injection of a particular tissue extract into a cat produced precisely the opposite effect. The blood-pressure did not fall, but actually rose, the heart was stimulated, and there were no signs of prostration. The extract with these remarkable properties was one made from a very special organ, the suprarenal gland (Fig. 52). Later investigation showed that the substance responsible for the effect was a definite chemical compound, now called adrenaline, which was ultimately isolated, its constitution elucidated, and its synthesis finally effected in the laboratory. This proved to be but one of many hormones, substances produced in certain organs of the body, secreted into the blood-stream and employed to control the activity of tissues at a distance. The molecules of these

substances act as messengers, as it were, sent out at the appropriate time to co-ordinate activities of the various bodily organs. Being carried along in the blood-stream and dependent on the latter for their transport, the hormones are much slower in developing their effects than the nerves. On the other hand, once this action has begun, it usually persists for some minutes or even hours or days (as in the case of thyroxin), and for this reason they are especially concerned with those activities of the living organism for which duration, but not speed, is essential. It is therefore not surprising that in the control of the various mechanisms associated with reproduction the hormones should play a highly important part.

For thousands of years man seems to have been acquainted with the effects of the removal of the testes (Fig. 52) in the young male. Growth continues, but not quite normally. The sinewy, angular frame of the typical male fails to develop; instead, there is a tendency to plumpness and even a suggestion of femininity in the figure. The size of the adult is usually abnormally great, a fact which has been made use of by the stock breeder when he castrates the animals which he intends to fatten for the market. But the most striking results of castration are those we read of as characterizing the eunuchs of Egypt and Rome and the Eastern courts. There is no development of the beard and the other "secondary" sex characters. In particular, the voice fails to break, a fact which made it possible to introduce adults with soprano voices into church choirs, from which females were excluded.

The removal of the testes, therefore, brings about two sets of results which should be carefully distinguished. On the one hand it makes impossible the formation of spermatozoa and so renders the individual infertile. But it also produces the various secondary effects referred to above, because the testes also produce hormones which act on the body controlling the development of what are called the secondary sexual characters. Naturally the second class of effects is the more pronounced the earlier in life the testes are removed; and it is

only when the operation is suffered before puberty that the voice retains its boyish character. These secondary characters, it should be remarked, are not essential to the bisexual type of reproduction. Some of them, indeed, are concerned with bringing together the ovum and spermatozoon; others, however, promote the prenatal and post-natal care of the offspring; and the actual union of spermatozoon and ovum (the characteristic feature of sexual reproduction) could take place in the absence of them all.

How many of these sex hormones are there and what is their chemical nature? Before any substantial advance could be made towards answering these questions it was necessary to devise methods for the detection of the substances in question and for measuring, at least roughly, their amounts; it is so often the case in science that advances of knowledge depend on the development of simple and reliable methods of detecting and measuring. A suitable test subject for the male sex hormone was ultimately found in castrated young cocks—capons, as they are called. Administration of certain tissue extracts to these birds stimulates the growth of the comb, and a test approximately quantitative in character based on this fact was developed. It was found that urine from males contained a comb-stimulating principle, and before long a crystalline compound was isolated which was active in very minute doses. It was named androsterone, and though it could be obtained only in very small amounts—one thousand litres yielded only 40 milligrams—its constitution was soon completely elucidated. Later a second and still more active compound was isolated from testicular tissue itself; it has been named testosterone. The former compound may be a by-product produced during the synthesis of the latter, and eliminated by the kidneys, though it is possible that both compounds may function in the body as sex hormones.

The reader may be wondering why a substance which promotes the growth of cocks' combs should be found in the tissues of men. The answer, of course, is that the cock's comb,

like the stag's antlers and Henry VIII's beard, is a secondary sex character, and the hormone that we are discussing exerts an effect on the development of secondary male sex characters in general and so acts on comb, antler, and beard impartially.

It has been wittily remarked that for the male, sex has the significance of a comma, but for the female it implies a full-stop. The relatively greater importance of reproduction in the female is, of course, particularly pronounced in the case of the mammals. The female organism has been specialized in various ways for reproduction, and this specialization powerfully affects its whole being—its anatomy and its physiology, its emotions, and its habits of life. It is not surprising, therefore, that sex hormones should be even more important to the female than to the male. These chemical hormones not only control the regular and essential cyclic changes which occur in the normal non-pregnant female, and prepare the way for pregnancy, but also direct and correlate the extraordinary developments which occur in the maternal organism once pregnancy has begun.

In this connexion one of the most important organs of the body is the pituitary gland (Fig. 52). If the brain is rather like a central telephone exchange, connecting up the various nerves which enter it from different parts of the body, this small organ is the Home Office, sending out messages via the blood-stream to various tissues throughout the body, and exercising a general supervision over all that is going on. It has two main departments, the anterior and the posterior lobes. It is the former which is chiefly concerned with sex activities and it acts principally by means of hormones which carry messages to the ovaries (see p. 233). It is thus that the pituitary gives the command to the latter to set about their main business, that of manufacturing ova ready for fertilization. But the pituitary gland also directs the ovaries in certain subsidiary but very important functions. It stimulates them to produce and secrete their own hormone; that is to say, to exercise a kind of delegated authority. When these new

instructions are obeyed the whole female organism becomes keyed-up for the process of fertilization. The compound produced by the ovaries which is responsible for this remarkable result has been isolated and obtained in a pure crystalline condition, and has been named oestradiol (*oestrus*, rut or heat). It was the discovery that this compound, or rather a closely related one, oestrone, with a similar action, could be obtained in relatively large quantities from the urine of pregnant women (and, curiously enough, even better from the urine of stallions) that made rapid advance possible in the chemistry of this group of sex hormones.

The changes which occur in the maternal organism after fertilization of the ovum and during the antenatal growth of the child are still far from being completely elucidated. It is already clear, however, that these changes are in large measure controlled by specific hormones, and that these messengers sent out by one organ at the appropriate moment stimulate others to activity, or perhaps inhibit them if they are already in action. In this way the exceedingly complicated series of stages is controlled and kept in step. It will doubtless be a long time before all the details of the story are deciphered, but some points have already become clear. First of all, however, a word is necessary about the development of the human ovum. An ovary which is about to produce an ovum first develops a small water-filled cavity called a follicle, and it is within such a follicle that the ovum develops. As it ripens, the follicle moves to the surface of the ovary, and finally bursts, expelling the ovum which finds its way towards the uterus as a preliminary to fertilization. It might be thought that the burst follicle had now finished its work, but that is not so. It remains on the surface of the ovary and under the direction of a pituitary hormone, develops into a factory—the *corpus luteum*—for the production of a compound called progesterone. Progesterone is itself a hormone, and it has the function of acting on the uterus so as to make it ready to nourish the fertilized ovum. If the ovum is in fact fertilized

and starts to develop, it seems able, presumably by means of another chemical agent, to ensure that the corpus luteum shall persist, and so makes certain that the supply of progesterone necessary for its own survival is kept up. In the absence of fertilization the corpus luteum fades away and the uterus returns to its normal resting condition. This return of the hypertrophied uterus to its resting condition involves the shedding of the extra tissue with a certain amount of haemorrhage: it is, in fact, the phenomenon called menstruation. It is about two weeks later that the ovary again produces an ovum, with the production of a new corpus luteum, and it is only during the three or four days centred round this event that the female is normally capable of being fertilized: a fact of which advantage has sometimes been taken for the purpose of preventing conception. If the corpus luteum is removed surgically during the course of a pregnancy, the uterus is left no longer under proper control and abortion may occur.

As the pregnancy draws towards its term, new developments take place in preparation for the birth itself and the suckling thereafter of the child. Obviously a highly complicated mechanism is involved, one of great potential danger to both mother and child should it be inaccurately controlled. The details of these complex processes are still obscure, but sufficient is already known to make it certain that hormones of various kinds play an essential part in regulating and correlating the events. Thus, the posterior lobe of the pituitary manufactures a substance which causes the pregnant uterus to contract, but the ease with which this effect is produced is influenced in various ways by the presence of oestradiol and progesterone. There seems, in fact, to be a whole complicated system of inhibitions and relays holding up or promoting an involved series of reactions. This branch of knowledge is still very young, but it is growing rapidly; in a few years, no doubt, we shall learn many of the details which are still obscure.

In the normal course of nature the mammalian mother suckles her young. As pregnancy terminates, lactation must

begin. The latter is itself a highly complicated process; it involves the production in the mammary gland of a fluid quite different from any of the other products of animal metabolism —a fluid containing everything necessary for the healthy growth of the young offspring, and manufactured in quantities amounting to pints per day in the case of a woman and gallons in the case of a cow. The mammary glands which carry on the special task of elaborating this unique fluid must be carefully regulated so that they are ready to begin their work when birth takes place.

For the control of the developing mammary glands the organism seems to depend on the same two hormones which play so important a role in the other processes connected with reproduction—oestradiol and progesterone. The former sees to the earlier stages; the growth and development of the glands at puberty and their subsequent maintenance in a suitably prepared though relatively quiescent condition. The latter comes into play during pregnancy itself and, in co-operation with oestradiol, controls the final development of the mammary gland and brings it into a condition ready for activity. But the actual signal to start producing milk in quantity comes directly from headquarters. The pituitary gland sends out a special messenger for this purpose. Amongst the many hormones which it produces, one, secreted by the anterior lobe, has the property of stimulating the mature mammary gland to function. This principle has therefore been called "prolactin". Its action would seem to be inhibited by oestradiol—the mutual antagonism of various hormones is a phenomenon constantly met with in this branch of science—and it may be that the synchronism of the beginning of lactation with parturition is ensured not so much by extra production of prolactin at the critical moment as by the rapid fall in the production of oestradiol which takes place during and immediately after the birth of the child. The prolactin which on this view is already present, is then no longer inhibited in its action and so the secretion of milk commences.

It is interesting that prolactin not only controls the secretion of milk, but is also responsible for "maternal behaviour" such as is exhibited by lactating rats and broody hens. It may seem surprising that prolactin should have any effect at all on a bird, but there is other evidence that prolactin is of importance in the lives of animals other than mammals. Thus it stimulates the crop glands of the pigeon, causing them to develop and to produce the "pigeon-milk" wherewith to feed their young. It is possible that this hormone was elaborated in the pre-mammalian world to initiate and control various aspects of maternal activity. From this point of view the control of lactation is merely a specialization of a previously existing device, an example of the type of thing so often found to occur in nature. The fact that the peculiar emotional state and psychological reactions associated with maternity are initiated and controlled by a chemical substance capable of being extracted and kept in bottles is one which will provoke satisfaction or dismay according to the natural bias of the reader.

An interesting and important application of our knowledge of the sex hormones concerns the diagnosis of pregnancy. It is now possible to ascertain with a high degree of reliability whether a woman is really pregnant or not, even as early as the second or third week after conception. It is necessary only to inject a small quantity of her urine into an immature female rabbit or guinea-pig and after a suitable time to kill the animal and examine its ovaries. This method of diagnosis (the Ascheim-Zondek test) sounds reminiscent of the prognostications of the Roman augurs, who foretold the future after examining the entrails of a suitable bird or beast, but it differs at least in this respect, that it gives the right result ninety-nine times out of a hundred. The method depends on the fact that whilst the pregnancy lasts the urine of a pregnant woman always contains a substance which can stimulate the immature ovaries with the result that they produce an ovum. This substance is presumably "spilled over" from the blood through

the kidneys and is probably derived from the placenta—though what its function may be in the woman's own body is not definitely known.

The fact that sexual activities are controlled by very small quantities of certain chemical substances, some of them of relatively simple composition, is a striking and perhaps disquieting result. Evidently in this field a little learning may be a dangerous thing, though full and accurate knowledge is likely to prove of the greatest value to mankind. Already preparations of the sex hormones are on the market, and they are being used in the treatment of various disorders occasioned by a deficiency or lack of balance of these internal secretions. Some of these commercial substances are extracted from the appropriate glands of animals; others are prepared by chemical processes in the laboratory. Just as in the case of the vitamins, the practical importance of the work of the biochemist on these hormones has been recognized by great Continental chemical firms who have liberally subsidized much of the work carried out in this field—and largely covered the result by patents.

The practical significance of the recent advances in the domain of the sex hormones is especially emphasized by the discovery that oestrogenic activity is not confined to the naturally occurring compounds, such as oestradiol and related substances, or even to compounds belonging to the same chemical type, but that synthetic compounds, some of them of relatively simple constitution, are also active. True, these synthetic substances do not in general possess the same great activity as the highly specialized compounds developed by the mammalian ovary; they are skeleton keys which do open the lock, though not quite so easily and smoothly; but the relative simplicity of their molecules makes them easy of manufacture. Besides, they may be produced with many variations of molecular structure, and the opportunity so afforded of correlating structure with activity should enable an insight to be gained into the design of key best fitted to open the lock; and ultimately we may hope to see on the market skeleton keys which

work as well as or even better than the complicated ones which occur in the organism. In the field of dyestuffs or of local anaesthetics or of plastics the synthetic chemist has not only imitated Nature: he has sometimes even surpassed her. It is not impossible that in the field of the sex hormones he will be equally successful.

MANDIR OFFICE

CHAPTER XV

ON GROWING UP

THE phenomenon of growth is the wonder of the poet and the last resort of the vitalist. Of all the features which distinguish living things, it may claim to be the most characteristic and also the most mysterious. The fertilized egg-cell begins to divide and increase; methodically it goes through stage after stage until it becomes the fully mature mouse or worm or man. Each individual grows, according to his species, in size, in shape, and in internal organization. Sometimes errors of development occur, resulting perhaps in Siamese twins or in animals with two heads or six legs or even in quite non-viable monsters; but usually growth proceeds accurately, true to type, and the finished article is as well-nigh perfect as anyone could wish. The precision of detail in that bird you shot the other day or that fly you squashed was infinitely greater than could be found in any product made by the hands of man.

Small differences, of course, there are between individuals of the same species. Even "identical" twins, supposed to be derived from the same fertilized ovum, are not really quite identical. But these divergencies are relatively slight. Clearly the phenomenon of living growth implies a degree of co-ordination and control outside all ordinary experience. What is the chemical background of this remarkable phenomenon?

Growth is not a property of living things alone. Certain objects in the inorganic world can also grow, and of them perhaps the most remarkable are crystals. Everyone knows that crystals of sodium chloride or copper sulphate will grow in a saturated solution of the respective salt. Quite obviously there are marked superficial resemblances between this inorganic growth and the growth of living beings. Is the analogy wholly superficial, or is there perhaps some substantial similarity?

Inorganic crystals, like living beings, grow only when the environment is appropriate. There must in either case be available a supply of the necessary raw material—atoms or molecules or ions. The crystals of one compound all resemble one another, both in external shape and in internal structure, just as do the individuals of one species. In neither case is complete uniformity attained; individual crystals exhibit flaws and peculiarities of structure, just like individual animals. It is true that we are accustomed to think of an animal as growing up to a particular size and then remaining approximately constant, whereas there is no obvious reason why crystals suitably nourished should not get bigger and bigger indefinitely. But it must be remembered that certain marine animals appear to go on growing all their lives, whilst, on the other hand, anyone who has tried to grow really big crystals knows that the larger a crystal becomes the more difficult it is to encourage it to go on growing. Even if the experimental difficulties could be overcome, there would clearly be a limit to its growth, for it would become so big that it would break under its own weight.

It is now well-nigh a century since John Ruskin fascinated the young ladies of an English school with his story of the behaviour of inorganic crystals; since the *Ethics of the Dust* was published, many fundamental discoveries have been made and new domains of knowledge have been explored, but the architecture of crystals remains as interesting and wonderful as ever. The work of the Braggs and the many who have followed in their footsteps has made it possible for us to picture in some detail the structure of these strange, familiar objects.

We now think of a crystal of sodium chloride, for instance, as composed of positively charged sodium ions and negatively charged chlorine ions arranged in a regular and uniform order, so that each sodium is surrounded by chlorine ions and vice versa (see Fig. 10). The surface will then consist of sheets of ions all in perfectly regular array. They may happen to be all sodium or all chlorine or perhaps alternately sodium and

chlorine, according as to which face is chosen. The whole crystal is held together by the electrostatic forces with which these positively and negatively charged ions attract each other. In the neighbourhood of any chlorine ions in a crystal surface there are naturally forces which tend to attract any sodium ion which strays into the immediate vicinity. When the crystal is growing in a saturated solution, layer after layer of ions is arranged the one on the top of the other. Each ion is guided into its proper place by the forces exerted by the ions already in position, and these are such that there is always a tendency to complete one sheet before starting another. Once a new sheet is begun it seems to be easier for ions to be added at its boundary than for a second new sheet to be started. Thus, the crystal, as a whole, grows by sheets, and it retains its flat-faced, straight-edged, geometrical form. Though each ion is controlled only by its immediate neighbours and has no direct relation with distant ions in the same crystal, yet the crystal as a whole possesses a certain unity and individuality. It retains its characteristic shape throughout growth and remains an organized whole.

When we come to more complicated salts, the structure and growth of their crystals is to be described in similar terms. The crystals of organic compounds are likewise built up of molecules of the substance arranged according to some regular pattern. In this case, however, the forces which bind the crystal together are not the strong ones exerted by one positive ion upon others of the opposite sign, but the weaker ones which are found in the immediate neighbourhood of any molecule. As a result, crystals of organic compounds are usually much softer than typical crystals of simple inorganic compounds.

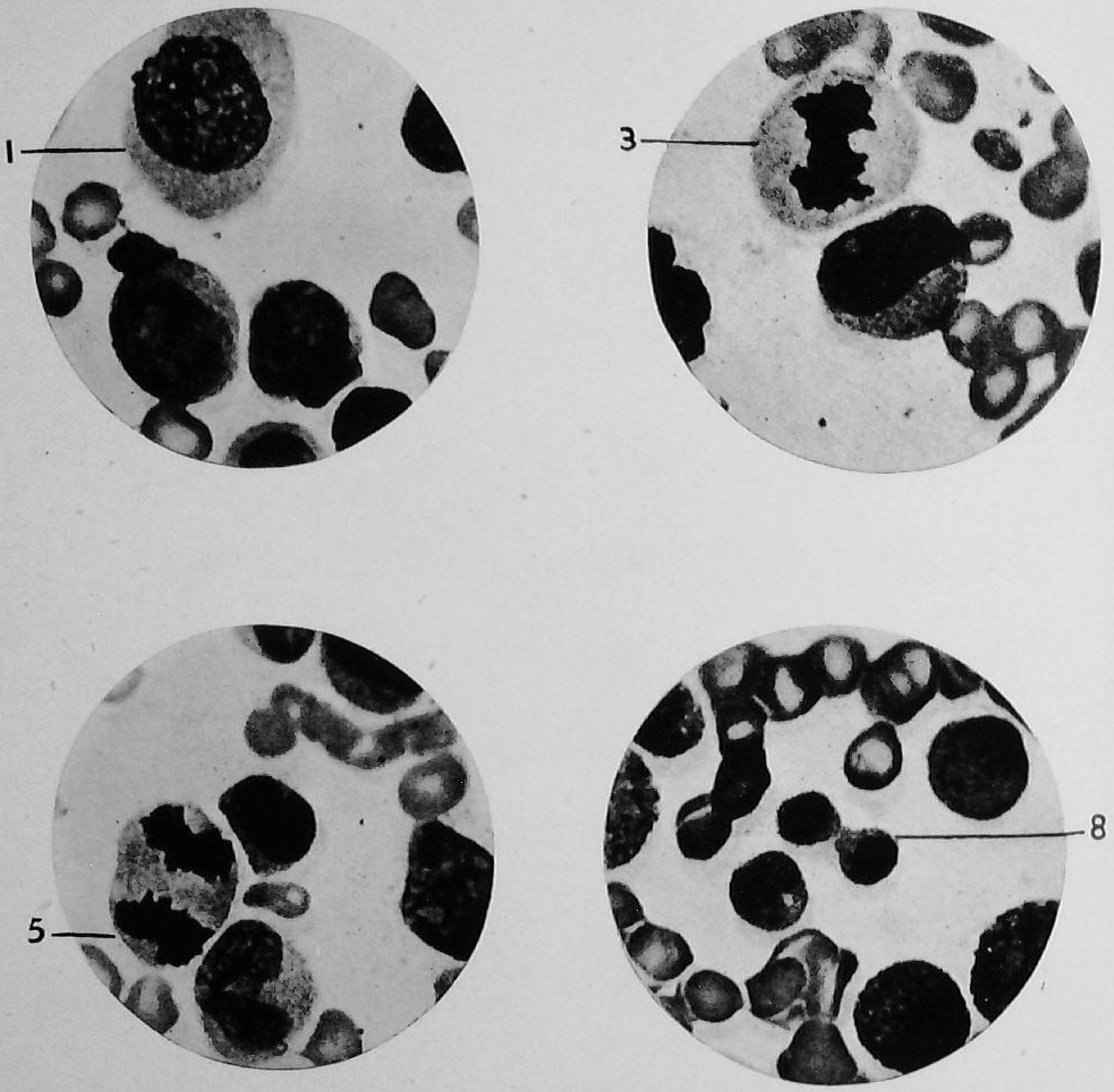
It is remarkable how selective are the forces which operate at the faces of crystals. Suppose, for example, a solution contains molecules of two kinds very closely resembling each other, that the solution is saturated in respect of both compounds, and that there are crystals of both in contact with

the solution. Under these circumstances it is usually found that each kind of crystal will select out of the solution its own type of molecule and will reject the others. In the case of complicated molecules, this principle sometimes breaks down—presumably these large molecules give rise to less highly differentiated fields of force—but, nevertheless, it is fundamental and of great practical importance. The organic chemist makes use of it daily when he crystallizes compounds to rid them of impurity.

When we come to *very* large molecules, we find that crystallization is usually effected only with difficulty. This is not surprising when we consider how awkward it must be to fit these voluminous, often unsymmetrical molecules into a compact, regular arrangement. Crystals of the native proteins are very unstable structures containing much water and tending to disintegrate when removed from the solution in which they have grown. The long-chain polymerides such as we discussed in Chapter VI could scarcely be expected to crystallize in the normal manner, for their great length renders them quite unwieldy. Instead, they often undergo a kind of two-dimensional crystallization: the thread-like molecules arrange themselves parallel to one another, and so form long fibrous bundles of regular cross-section. In all cases, however, the underlying principle is the same: the orientation of a newly acquired molecule by means of forces exerted by those already in the aggregate, and the extension, in this manner, of the pattern already in existence.

Now the last sentence might also be taken as a description of the process which occurs during the growth of living matter. No doubt the structures involved are very much less regular. The process of assimilation is usually much more complicated. Often chemical reactions are involved as a preliminary to the actual assimilation of the new material in the structure. The new molecules cannot be fitted in just as they are when received from the environment. It is no longer a question of building compact columns out of bricks of identical size and

PLATE V.



ILLUSTRATING THE PROCESS OF CELL DIVISION.

The numbers refer to successive stages in the process, of which four have been selected in this plate. (See p. 247).

(By permission from photo-micrographs taken by Lt.-Col. W. F. Harvey, Royal College of Physicians, Edinburgh).

shape; rather it is a matter of constructing a complicated edifice out of stones of various sizes, shapes, and varieties which must be hewn and carved to the exact design required. But the actual process of growth appears to be essentially a process of arrangement and fitting, in accordance with a pattern already existing and under the influence of the forces determined by that pattern.

In support of this point of view, we may invoke the general principle of reproduction—that like gives rise to like. One cell grows and divides and thus two cells are formed each very closely similar to the original one. But this general correspondence of structure becomes more definite and precise if we consider the most important part of the cell, namely the nucleus, with its component chromosomes, long filament-like structures (see Plate V) which, it is now generally agreed, determine the characters of the "daughter" cells. An essential preliminary to cell division is the division of these chromosomes, and it is found that the new chromosomes have just the same potentialities in determining future development as the old ones. It follows that they must have exactly the same molecular pattern: in other words, the molecular pattern must have doubled itself. It is difficult to see how this could happen otherwise than as the result of the original pattern inducing the development of a similar pattern, presumably in an adjacent molecular layer. The new layer would duplicate the old one in somewhat the same way as successive parallel slices of a crystal correspond to each other in pattern. This, at least, is a possible working hypothesis, and the broad facts do not seem to be easily explained in any other way.

Of course, when we come to the details of development in a plant or animal we have obviously a process of extreme complexity, and it is not surprising that our knowledge is still only rudimentary. Growth involves accurate co-ordination of the various parts of the organism not only in space, but also in time, co-ordination in four and not merely three dimensions. Most of the details of the very complicated mechanism which

controls these activities are still hidden from us, but already research has revealed some of the factors involved.

A typical example is afforded by the discovery by Went that an extract of the growing tips of various plants exercised a remarkable effect on plant growth. The effect of this extract is most conveniently demonstrated and measured by applying it to one side of the stems of decapitated young wheat shoots (see Fig. 53). Within a few hours the previously straight stem bends round in such a way that the treated surface is convex, showing that the extract must have induced extra rapid growth in the region where it was applied. Investigation led to the conclusion that the active extracts contained an organic substance which appeared to promote and control the growth (or, more precisely, the elongation) of plant cells. Interest was at once aroused as to the constitution of the active compound, but at first there did not appear to be great promise of rapid advance in this direction, for the quantities involved were evidently excessively small. However, an opportune discovery was made. It was found that urine sometimes contained the factor in relatively large amounts. It is particularly plentiful after a diet rich in vegetables, and it is evidently collected and excreted by the kidneys, presumably as waste material. By taking advantage, then, of the body as a factory for preliminary concentration, it was possible to isolate the active compound in a pure crystalline form and in relatively large amounts. "Relatively" must be emphasized, for even when large volumes of urine were handled the quantity of the compound obtained was

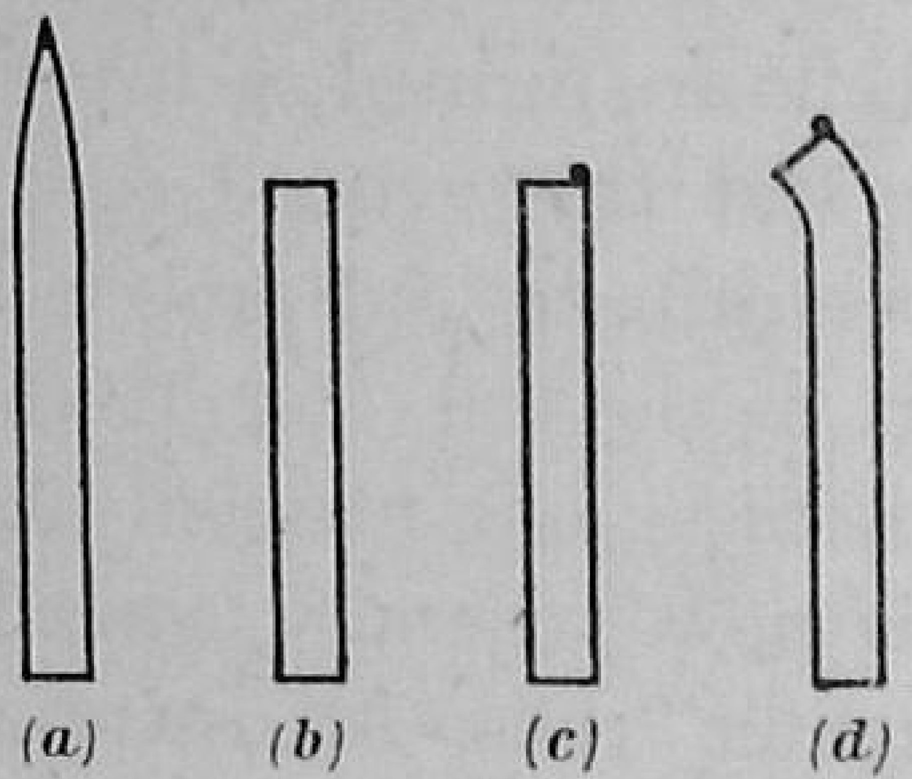


FIG. 53.—Illustrating the curving effect of the application of auxin to one side of a growing wheat seedling. The growing seedling (*a*) is decapitated (*b*), and a trace of the active material is applied to one side (*c*). This induces more rapid growth on the treated side, so that the tip bends over (*d*).

still to be reckoned only in milligrams rather than grammes. But the chemical investigation of auxin, as the new compound was called, was in the extremely skilful hands of Kögl and his collaborators. It is a striking testimony to their ability and also to the great advances made in micro-chemical technique that with only one or two hundred milligrams of auxin at their disposal they were able to deduce its quite complicated structure (Fig. 54). In the old days, the days before Pregl had developed the method of micro-analysis,

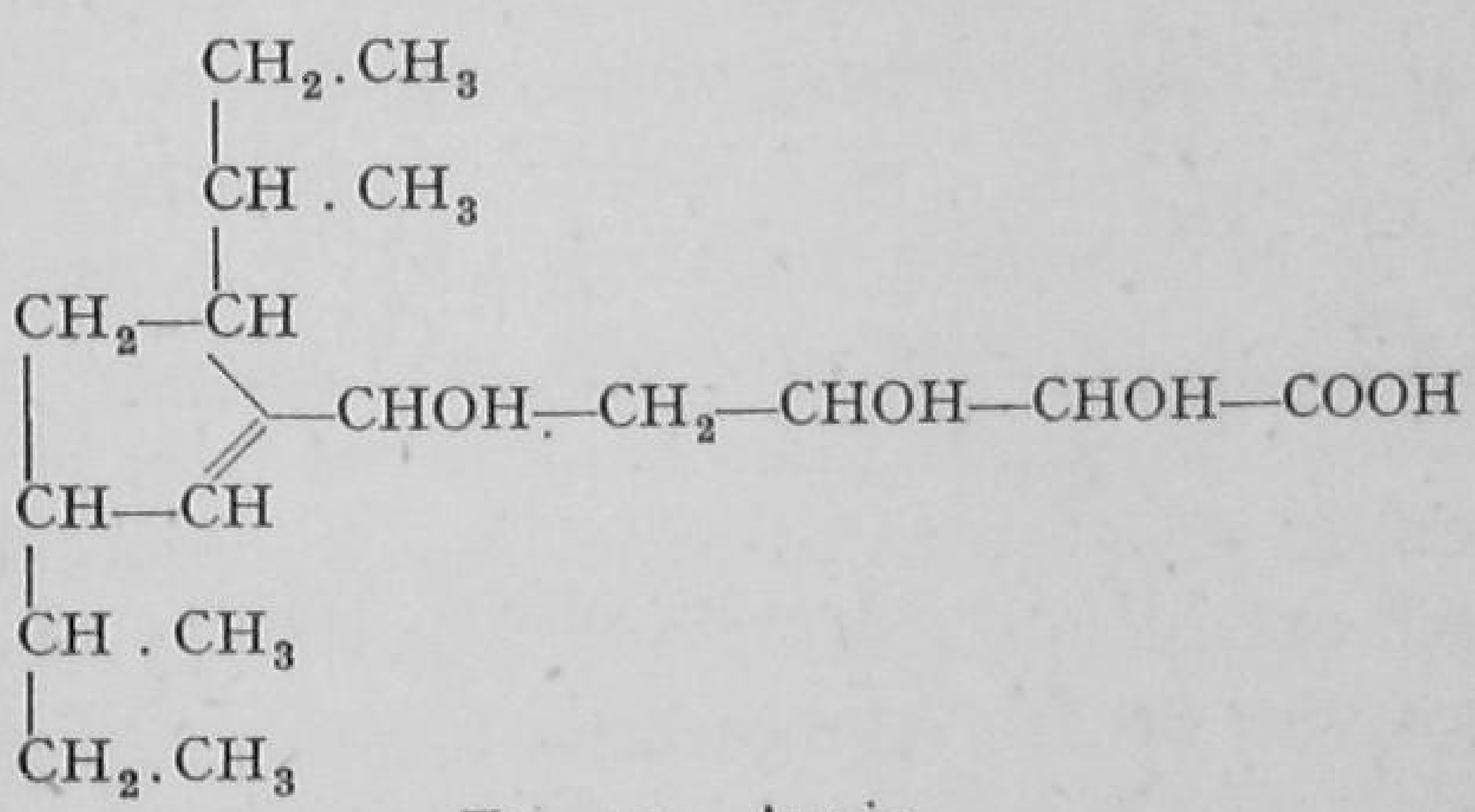


FIG. 54.—Auxin.

this quantity of material would scarcely have sufficed for a single estimate of its content of carbon and hydrogen.

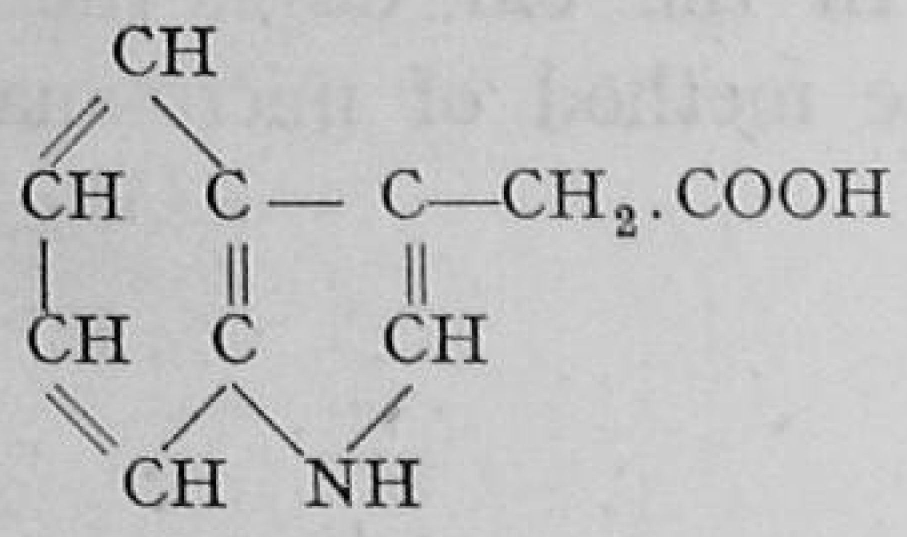
It was later found that urine may contain another and rather simpler compound which acts on plant tissue in the same way as auxin, and which is almost equally potent. This second compound proved to be an acid which is formed in the animal body, probably from the amino-acid trytophane (Fig. 55 *b*), and is called by the chemist indolyl-3-acetic acid. Chemical substances are often given strange, unwieldy names such as this, but these names act both as a label and also as an indication to the chemist of the structure of the substance. This second function of the name, as it happens, does not concern us here, but we have to use the awkward title, for it is the only one available.

There is no evidence that indolyl-3-acetic acid plays any role within the plant in regulating its growth—it is not found

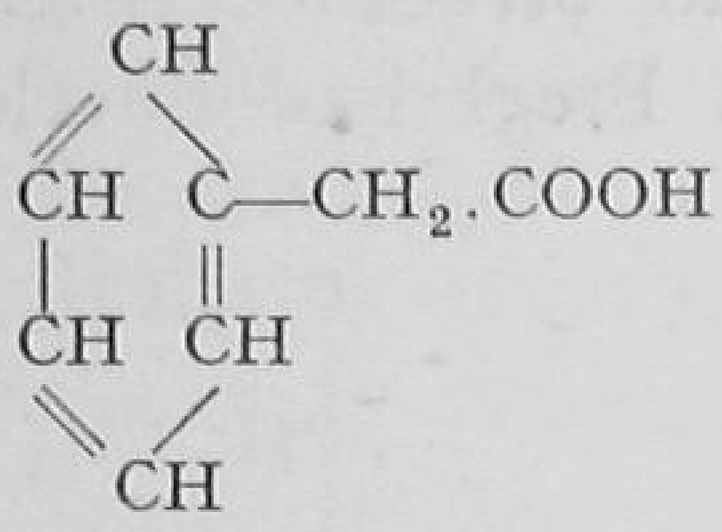
in the growing parts, as auxin is, and it is very puzzling why it should have this extremely potent action.

Both indolyl-3-acetic acid and auxin exert quite measurable effects on wheat shoots in dilutions of the order of one part in a thousand million.

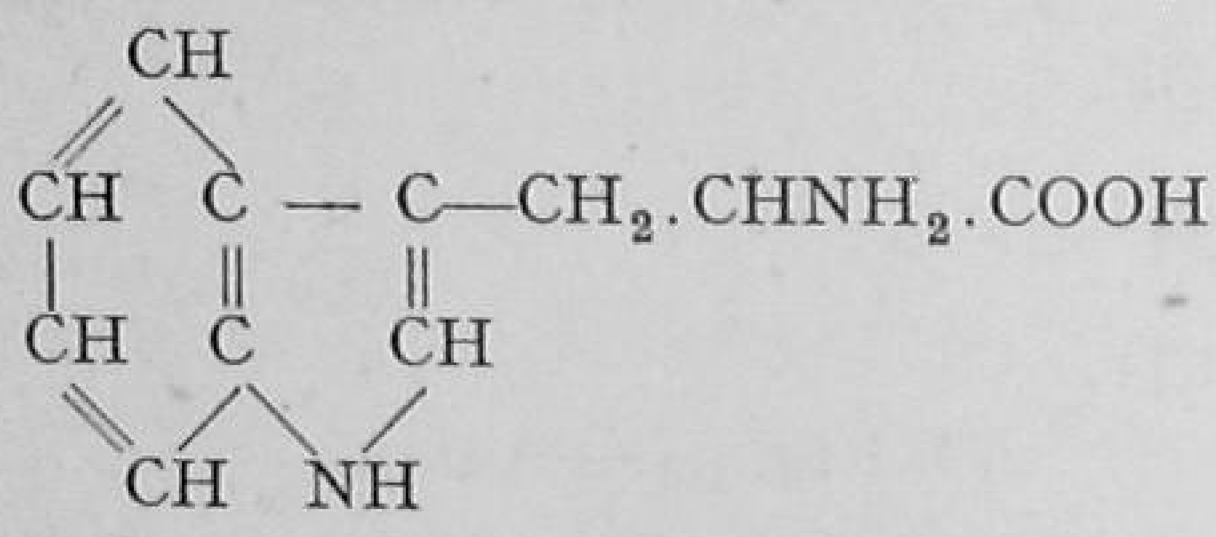
In recent years these chemical compounds which so curiously influence plant growth have assumed practical importance to



(*a*)
Indolyl-3-acetic acid.



(*c*)
Phenylacetic acid.



(*b*)
Tryptophane.

FIG. 55.

the farmer and the horticulturist. It is not auxin itself or indolyl-3-acetic acid which has found practical application, but, as so frequently happens, certain synthetic compounds, which the chemist, following up the clue furnished by the discoveries of Went and Kögl, has synthesized and had tested for biological activity. The useful products are, like indolyl-3-acetic acid, derivatives of acetic acid and are sold commercially under various trade names.

Three uses are worth special mention. Some of these compounds are particularly effective in stimulating the development of roots and are applied to cuttings to increase the proportion of successful "takes". Some have a remarkable action on certain varieties of fruit, and if used, for instance,

to spray tomato plants at the appropriate time, strikingly promote the setting of the fruit and so increase the crop. Other compounds exercise a profound influence on the general growth of many plants, causing their stems to twist and buckle and develop a grotesque and pathological appearance often ending in death. Rather remarkably only dicotyledons seem to be affected, so that if fields of corn are treated, many of the weeds are killed, but the corn grows with impunity. These helps to food production are the results of but a few years' work; the exploitation of chemical control of plant growth may yet lead to more profound and revolutionary changes in agriculture.

If the control of plant growth is of great economic importance, the problems of the development of animals and especially of man are of more personal interest. In man and most of the other higher animals we meet the striking fact that the growth of the body as a whole is limited to the earlier part of the individual's existence, perhaps to only a fifth or a tenth of the natural span of life. The fact that this compression of the growth period to the early fraction of life is specially characteristic of birds and mammals is obviously related to the reproductive habits of these animals. In mammals the young are born at a relatively advanced stage of development; in birds the egg contains sufficient food to enable this stage to be reached before hatching. Obviously the size of the newly born young or the newly laid egg must be considerable, and so it is an advantage for the mother to have done most of her growing before the attainment of sexual maturity. Whatever the explanation may be, this compression of growth into the earlier years of life, and its cessation thereafter, implies a very precise control over the growth of the body as a whole. Some insight into the means by which this control is exercised is obtained by examining the cases where the control has gone wrong. Most of us reach a height somewhere between five or six feet. What has happened in those individuals who are almost as small as

the Lilliputians or those who seem to be trying to rival the inhabitants of Brobdingnag?

We are not, of course, here concerned with those people who for hereditary reasons are somewhat above or below the average height, but rather with those giants and dwarfs who owe their abnormality to a definitely pathological cause. Many people are unduly short because in their childhood or youth their growth was stunted as the result of disease or defective nutrition (see p. 256). We have already met an extreme example of this in the "cretin" dwarfs, those physically weak and mentally defective children sometimes born in districts where goitre is common as a result of iodine deficiency (see p. 172). Here the cause is evidently the failure of the thyroid gland to function properly in the yet unborn child, with the resulting disturbance of the growth and development of body and brain alike.

Perhaps the most interesting types of giants and dwarfs are those in which the departure from normality is the result of a disturbance of the pituitary gland. We remarked in the last chapter that this gland appears to function as a kind of Home Office for the body. It is therefore not surprising that among the messengers sent out from it one particular group is concerned with the control of growth. Extracts of one part (the anterior lobe) may be prepared which when injected into young animals hasten the growth of the bones; these extracts of the pituitary gland evidently contain a "growth-promoting factor".

Now, in man, as in most mammals, cessation of growth is associated with puberty and the attainment of sexual maturity. Of the many bodily changes which then take place, one is an alteration in the growing parts of the bones which makes further lengthening impossible. The pituitary gland plays a dominating part in controlling and co-ordinating the many activities of the organism required for sex and reproduction, and so it is probable that in addition to the promotion of normal growth in childhood and youth, its secretion is also

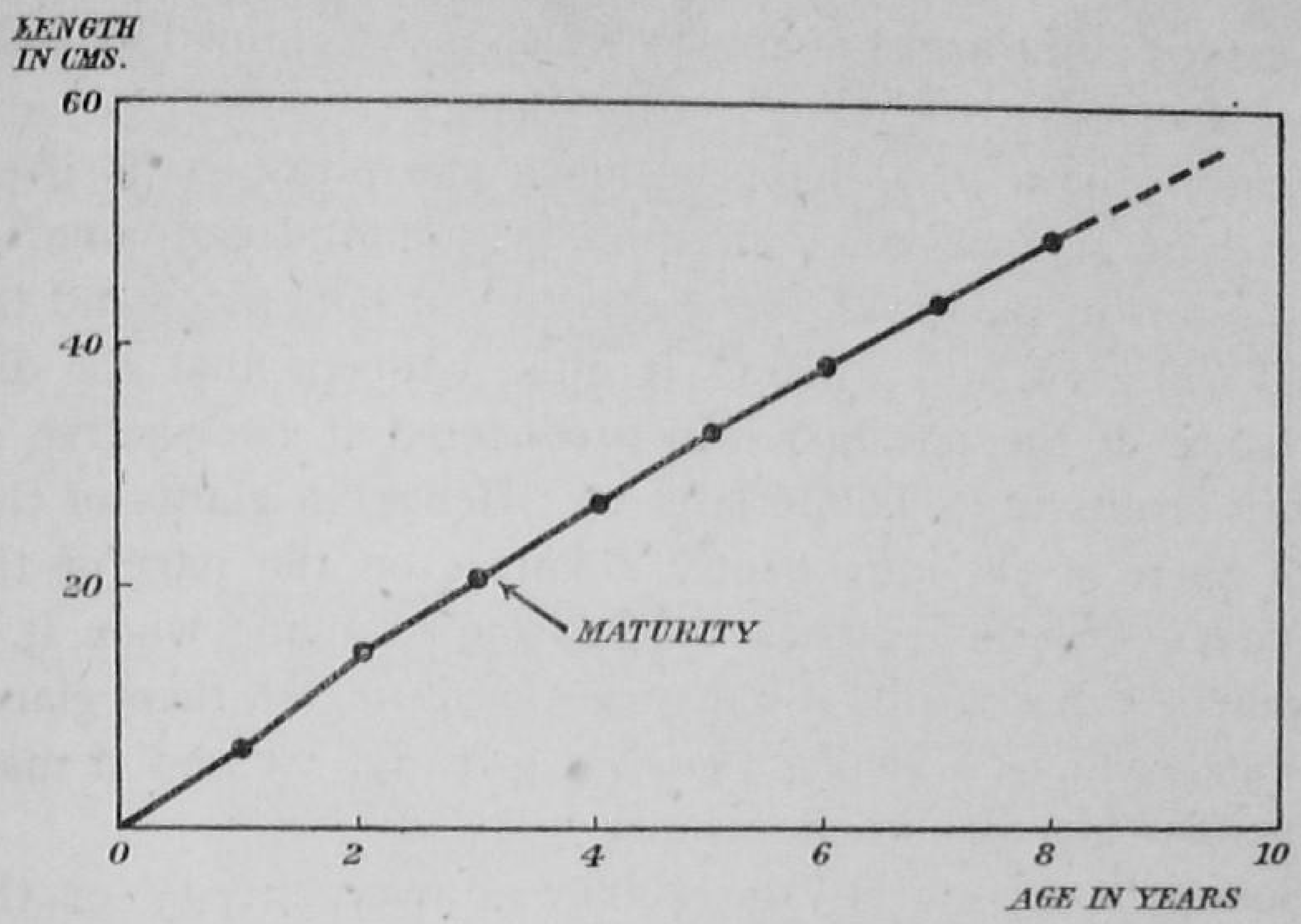


FIG. 56.—The line shows the average length of Loch Maree trout at different ages.
(From data given by G. H. Hall, *The Life of the Sea-Trout*, 1930.)

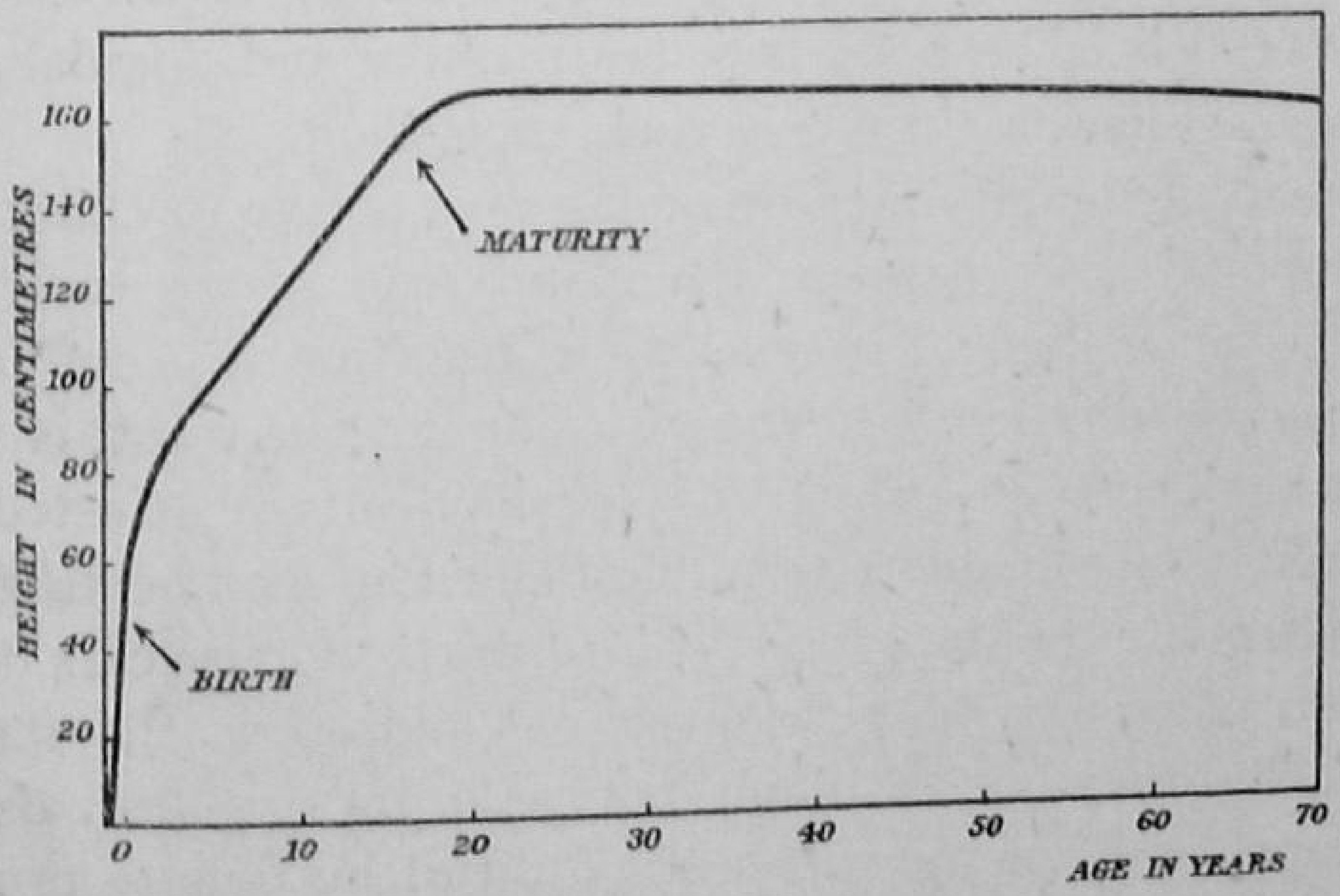


FIG. 57.—The line shows the average height of men at different ages. The virtual cessation of growth in man and most other mammals soon after puberty is in marked contrast with the progressive growth of fish and many other creatures throughout life.
(From data collected by Friedenthal, *Physiologie des Menschenwachstums*, 1914.)

concerned in the arrest of growth which is determined by these bone changes.

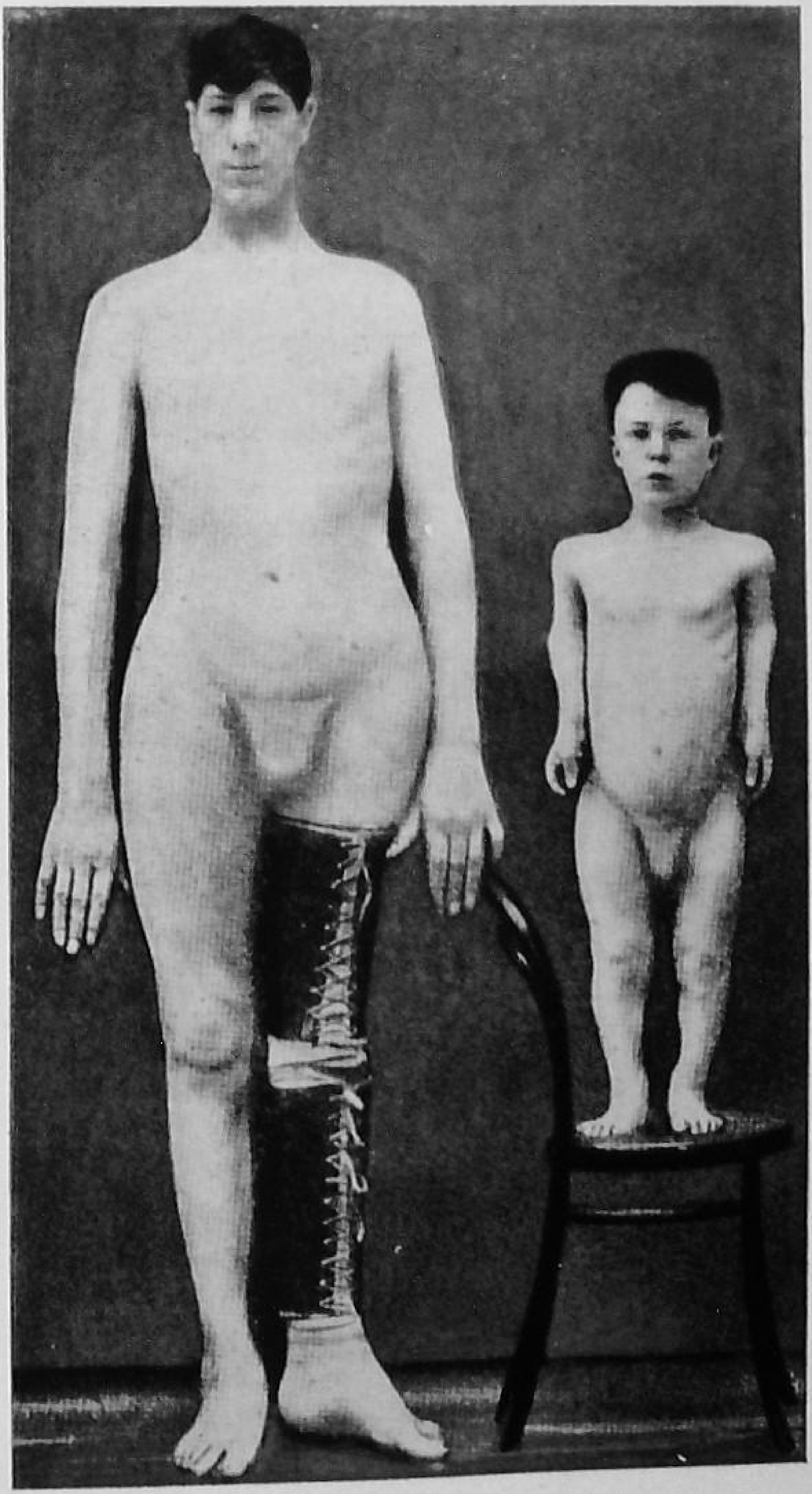
Consider now what happens when the pituitary is over-active and produces too much growth-promoting hormone. If this occurs in childhood, rapid growth will take place and the child will grow into a giant. It often happens that the disturbance of the pituitary which rendered it over-active in youth results in its failure later on. Hence, in giants of this type there is not infrequently a failure on the part of the pituitary to produce the sex-regulating hormone when it is required. Consequently it sometimes happens that these giants are undeveloped sexually; they are soft and fat and if male somewhat feminine in appearance.

Sometimes, however, the abnormal over-activity of the pituitary may not set in till after adult life has been attained. The bones are still able to respond to the growth-stimulating hormone, but not by becoming longer, for they have already set to a fixed length. The actual result is a peculiar and characteristic distortion of the skeleton known as acromegaly (see Plate VI). The body becomes massive and angular, and the face assumes a curious leonine expression.

Instead of the pituitary becoming over-active in childhood, the opposite may happen; the gland may at an early age undergo some kind of degeneration, resulting in a failure to produce its secretion in adequate amount. The result is what might be expected—growth and development are arrested and the individual remains a veritable Peter Pan who never grows up. These are the dwarfs of twenty, thirty, forty years of age or even more who play the parts of children on the stage—physically they are children not only in size but also in development. For the pathological pituitary fails to produce not only the growth hormone but also the secretion which initiates sexual maturity. A very different type of dwarf is produced when the bone changes which put a stop to their further lengthening occur prematurely. Sometimes this fixation of the bone length may occur not long after birth or even

Pictures showing successive stages in the onset of the condition of acromegaly.

(By permission from Schafer "The Endocrines.")



Acromegaly and Achondroplasia.

(By permission from Walton "Surgical Diagnosis".)

before it. The precise cause of this condition (called achondroplasia) is not known—it may possibly be due to some too early activity of the pituitary. In these individuals the body usually goes on developing more or less normally except that growth in the direction of length is curtailed. Development is limited to the other two dimensions, and so we obtain those burly, squat little fellows, the "Little Tiches" of the stage. They become fully developed men and women, often very strong and healthy, only ridiculously short.

Two other types of dwarf may be briefly mentioned. The first of these includes those miniature men and women, perhaps barely two feet in height, who are sometimes exhibited in fairs or on the stage. These "Tom Thumbs" are mature and perfect in every detail, only they are built on a reduced scale. Evidently some abnormality in development has taken place. The exact cause is not known; but here is a likely explanation. The fertilized ovum first divides into two cells, then into four, and then eight, and so on. If at such an early stage of development one cell becomes detached from the others, it may still develop into a complete perfect adult, but an adult of unusually small size. At least, this has been shown experimentally in the case of the developing sea-urchin's embryo, where one cell can be deliberately detached from the others and reared until it has developed into the miniature adult. It is a plausible guess that human midgets are the result of a rare embryonic accident of this kind.

The other type of dwarf to be mentioned starts as an apparently normal baby, but even in childhood begins to look prematurely old. His face becomes set and wrinkled and his growth is stunted. The wizened, senile young man is usually intellectually precocious and highly intelligent. The trouble in this case is thought by some to lie in the pineal gland (Fig. 52), that peculiar organ within the brain which the ancients thought was the seat of the soul, and which according to modern evidence has some obscure relation to growth. In these precocious dwarfs this gland, which normally decreases

in activity in early childhood, apparently continues to function at an undiminished rate, and the result is premature physical senility.

This discussion of dwarfs and giants brings out the importance, for the control of bodily growth, of the glands of internal secretion and especially of the pituitary. Another gland which seems to be of some importance in this connexion is the thymus. This organ, which is found in the chest (see Fig. 52), is peculiar in undergoing a decrease in size about the time of adolescence, when growth slows down and ultimately stops. There is some evidence that extracts of this gland promote growth and that removal of the organ during the period of growth has the opposite effect. Much work remains to be done before we can give a complete account of what happens to change the rapid growth of the boy of ten to the fixed size of the man of twenty, but it is already clear that special chemical molecules, synthesized by certain glands and secreted by them into the blood-stream, are essential factors in bringing about the change.

Of course, we must distinguish between the growth-stimulating hormones on the one hand and the vitamins which are necessary for growth on the other. The latter happen to be indispensable components of living cells; in the absence of a sufficient supply of the necessary molecules the normal number of cells in the body cannot be manufactured. There is no evidence that vitamins exercise any specifically stimulating action. It is true that the addition of half a pint of milk per day to the diet of the ordinary schoolchild is found to increase his growth rate appreciably, and this in spite of the fact that he is already an inch or two taller and a pound or two heavier than his father was at the same age. But this just goes to show how miserably nourished and how stunted the average child used to be—and sometimes still is. There is no evident advantage in size *per se*; what is important is the realization that previous standards of environment and diet have been inadequate to bring out the full potentialities of the growing

organism. The best seeds will do badly in poor soil; manuring the soil improves the plants, but only to the limit set by the quality of the seeds; in the same way, an excess of the growth-promoting vitamins will not produce giants. The hormones, on the other hand, have a positive effect: they stimulate the cells and modify their behaviour; they are active controlling agents.

So far we have been concerned only with the growth of the body as a whole and of certain gross structures such as the bones. But this is evidently only the fringe of the problem. It is the development of detailed structures which appears to be more mysterious. How does the newt contrive to grow a new leg from the stump of his old one? What are the forces which constrain the multiplying cells of the developing embryo to form themselves into head and eyes and hands and legs, and all the other complicated structures of the fully developed body?

It is indeed in the course of embryonic development that we meet with the problems of growth in their most challenging and dramatic form. Here in a hen's egg is a fertilized ovum, entirely master of its fate and depending on the rest of the egg only for its supply of food; within three weeks this single cell will have grown into a complete and perfect chick. All the time the embryo has been growing, it has been demonstrably isolated within its shell from all outside control. This miracle of embryonic development presents one of the most fascinating of all the problems of science.

We are still in a position to form only a very incomplete picture of this complex process. However, thanks in large measure to experimental observation on the growth of the embryos of newts and other amphibia, a great deal has been learned of the general line along which development proceeds.

A classical experiment in this field of research was the demonstration in 1924, by the great German experimental embryologist Hans Spemann and his pupil Hilda Mangold, that tissue from a special region near the end of the embryonic

gut, "the dorsal lip of the blastopore", transplanted on to the already differentiated parts of another embryo, initiated in the latter the development of a second, parasitic, embryo. This particular tissue has apparently some power of controlling and organizing into a new form the cells in its immediate neighbourhood.

Soon it was discovered that cell-free extracts retained the potency of the original tissue, and that these extracts could be boiled and subjected to chemical treatments of various kinds without being inactivated. Much more surprising was the discovery that extracts made from a variety of tissues, themselves inactive, had the organizing power hitherto associated with the special embryonic tissue. Indeed, it was soon realized that suitably prepared extracts of almost any ordinary tissue showed activity as an "organizer". Evidently most tissues contained a factor, relatively stable to heat, which is normally combined with some other cell-constituent and is only liberated after suitable treatment. It was shown that this active factor was extracted by ether, and it was ascertained that it belonged to that fraction of the ether-soluble constituents of the cell not hydrolysable with sodium hydroxide solution. These and certain other of its properties suggest that it belongs to the sterol group (see p. 284) of organic compounds, and is therefore related to vitamin D, the sex hormones, and the bile acids. It is an interesting fact that certain synthetic compounds of the class which possess cancer-producing (carcinogenic) and oestrus stimulating (oestrogen activity (see pp. 237, 284, 289), can also act as organizers, the organizer activity being specially associated with oestrogenic action. Whatever the "organizer" compound present in animal tissue may ultimately prove to be, it seems beyond doubt to possess a relatively simple molecule analogous to the sex hormones already discussed. This must be one of the key compounds in the process of growth and development.

This chemical compound, the organizer, may be thought of as analogous to the guard's whistle which starts the train.

It induces the undifferentiated, unorganized tissue to organize itself as an independent embryo. But once this fundamental orientation has taken place, once the train has been started, how is the development kept on the right lines? The young embryo is at first little more than a tube or axis. A definite orientation soon begins to manifest itself. One end commences to develop into the head region, the other into the trunk and tail. It is through experiments on the embryos of newts at these early stages that results of great importance have been obtained. If a piece of tissue be removed from the tail region of one embryo—this in the ordinary course would develop into tail organs—and is grafted on the head region, it will usually develop not into tail but into head organs. Conversely, tissue from the head region grafted into the tail end of an embryo will tend to develop into tail organs. Evidently the embryonic tissue has a certain plasticity—its course of development is greatly influenced by the environment in which it finds itself.

But this plasticity is only relative. Once development has proceeded so far, tail tissue can only develop tail organs and nothing else. The tail tissue becomes irrevocably destined for the hinder parts, but within these limits it still retains its former plasticity: it can still develop indifferently into a leg or a tail. But once growth has proceeded a little further, then the tissue becomes more specifically assigned—it is now definitely part of a leg and cannot develop into anything else. It is still plastic, however, with regard to the various parts of the leg. But gradually these different parts differentiate themselves out, and as they do so the tissues of which they are severally composed become ever more definitely fixed in respect of their future development.

It is perhaps an undue stretching of the imagination to compare to this extraordinary process of organic growth the relatively simple development of an inorganic crystal. And yet the analogies are obvious enough. The initiation of crystallization is often a peculiarly difficult process. A nucleus or

"seed" is required, a trace of the crystalline material, a fragment of the regularly arranged atomic lattice, the forces emanating from which guide the new atoms into their correct positions. And once the crystal has begun to grow and acquired a definite form, the new material which it takes into its system arranges itself in the correct way, forming planes and edges and corners, all in their regular order, and these in their turn guide still other atoms into their correct positions. In a complex crystal pattern, such as the ice crystals found in snow, the whole pattern is gradually developed in its full complexity from a smaller and simpler form. As with the growing embryo, there is a slow differentiation of the parts from a more general primitive type. In the biological case, of course, the atomic patterns involved are almost infinitely more intricate. In the fertilized germ cell, from which the whole process of growth starts, we have a complicated arrangement of organic molecules. This unique and intricate structure has very special properties, and pre-eminent among these properties is the ability to grow and develop in the way described. This means that the molecular patterns in a group of cells at some particular stage in the development of the embryo is such that new material coming into the system is arranged as an extension and development of the same pattern. The new tissue thus formed in turn co-operates in the organization of further material, and thus we get the progressive growth and development of the organism.

One is reminded of the behaviour of small particles of iron scattered on a piece of paper immediately below which has been placed a small magnet. If the paper is gently tapped, the iron particles arrange themselves so as to form numerous lines running from one pole to the other. If the arrangement is disturbed, the same picture will re-form itself provided the gentle tapping is continued. The iron filings, in fact, map out the so-called lines of force of the magnetic field. It is not suprising, then, that it has become customary to think of the organizer regions as exerting "determining fields" in their

immediate neighbourhood, and of the various parts of the growing embryo as developing in the appropriate "field". Consequently, grafted tissue, if sufficiently undifferentiated, will be moulded into a configuration determined by the local field, just as a fresh batch of iron filings will settle down into a pattern in conformity with that already existing. The fact that the iron filings are not entirely passive, but, being small magnets themselves, slightly modify and intensify the field in their immediate neighbourhood, has an obvious if somewhat fanciful analogy to the fact that the embryonic fields become more and more differentiated as developments proceeds, and in turn induce the differentiation of new fields.

New structures are formed not only during embryonic growth; very similar and almost equally puzzling problems are presented by the phenomena of the regeneration of organs —by the crab which grows a new toe or the lizard which produces a new tail. How is it that the new tissue knows what form to assume and to what size to grow? Some light is shed on this question by the very interesting experiment in which the nodule which formed on the stump of the amputated leg of a lizard, and from which the new leg would normally have grown, was grafted on to the stump of the amputated arm. The leg tissue developed to form part of the new arm. Evidently its growth was determined not so much by its innate make-up as by the environment in which it found itself. This suggests once more the existence of "fields" of some kind, located in particular organs and tissues and their immediate neighbourhood, and guiding the growth of new tissues within the space over which the fields extend.

It would seem, then, that we must think of the detailed structure of living organisms as developing under the influence of "fields , determined by the organized tissue already present, and gradually growing in extent and precision as more and more organized tissue comes into existence. We may feel uneasy, however, as to whether these "fields" *really* explain the phenomena in question. They are slightly reminiscent of

the explanation of the soporific effect of opium as being due to its "virtue dormative". It may be suggested that the explanation in terms of the so-called "fields" is nothing more than a description of the facts and that we are simply using a form of words to mask our complete ignorance of the real nature of the phenomena. There is doubtless some force in this contention; but it must be remembered that, as explained in Chapter II, all science, in the ultimate analysis, is only a description of the facts—a description as true and at the same time as comprehensive as possible. The statements made must have maximum reliability and also maximum content. Now the trouble about *ad hoc* explanations, such as the description of the phenomena of regeneration and embryonic development in terms of "fields", is that they are of relatively limited content. They apply only to a special set of phenomena and they are not applicable even to these in a quantitative form. Thus they lack both generality and precision. This is really the fundamental objection against these explanations of living phenomena which are vitalistic in type, that is, which explicitly or implicitly postulate a "spirit" or "entelechy" or some such notion. Similarly, it is the objection to theistic explanations of the universe as a whole. Such explanations are not necessarily wrong, they are merely scientifically somewhat empty and uninteresting. However, as the conception of these "fields" does correlate a considerable number of facts and has a qualitative, though not a quantitative, content, it is acceptable at least as a provisional interpretation of the facts.

In the final analysis, of course, we hope to describe such a "field" in terms of the properties and reactions of the various cells which determine it, and these in their turn in terms of molecular structure. The magnetic field round a magnet was similarly explained in terms of the elementary magnetic properties of the individual iron atoms, and later these were interpreted in terms of electron orbits and quantum numbers. We may expect these biological "fields" to be analysed

ultimately in terms of enzymes or diffusing hormones or metabolic rates. The structures and processes involved are evidently so complex that the elucidation of detail is likely to be a long and tedious task. It involves the most delicate and specific properties of highly organized aggregates of billions of billions of atoms.

It is not surprising that so immensely complex a structure has extraordinary properties; that it can grow and reproduce and repair itself. But how does it actually work? Our human minds are reduced to the study of its separate parts, in the hope that the understanding of these relatively simple parts will help us to understand the whole. But the very process of analysis destroys what is perhaps the most important thing of all, the mutual relations, the co-ordination of the parts, the integration into a whole. Perhaps a new scientific technique is needed to deal with such wholes; perhaps they are fundamentally outside the range of the scientific method and must be left to the artist and the poet to fathom and interpret. Certain it is, however, that the limits of the scientific approach have not yet been reached; and the biochemists of this and many future generations have still an ample hunting ground full of interesting facts and curious relations, and how far this will lead to complete understanding no one can say. "To travel hopefully is better than to arrive."

CHAPTER XVI

CHEMICAL MAKESHIFTS IN NATURE

NATURE is full of makeshifts of one kind or another. Structures designed primarily for one purpose may subsequently be adapted to quite different uses. Take, for example, the development of limbs. When our ancestors lived in the sea, they used their appendages for swimming about in the water. It was only when they emerged and began to spend a large proportion of their time on land that it became highly advantageous to be able to walk or hop or run about, and so under the influence of natural selection, the finny appendages were modified into limbs. In the frog, the limbs are dual-purpose instruments, useful for jumping on the land and swimming in water. Some reptiles (now extinct) developed wings and learned to fly, one of them at least with such success that its descendants have become the birds of to-day. In the majority of mammals, all four limbs have been highly specialized for walking and running; the horse, the sheep, the pig, or the elephant come to the mind. But cats use their claw-bearing paws for catching mice and playing with balls, and we have all seen the racoon in the Zoo busily washing its food with its fore-paws. The sea-lion has converted its limbs into flappers, while bats, like the birds, have transformed them into wings. The monkeys and apes have avoided the specialization characteristic of most mammals. They employ their fore-limbs to assist in locomotion, but make much use of them for grasping objects in the manner of hands. In man the fore-limbs are not used at all for locomotion. They have developed as instruments for exploring and controlling the environment; they have become the chief executive officers of the human brain. The hands of the billiard player who makes a break of a thousand, of the expert typist, or the pianist, with his exquisite

delicacy of touch, are remarkable examples of adapted structures well-nigh perfect in their performance.

These anatomical adaptations are familiar to all students of biology. They are staring us in the face and need only be pointed out to be appreciated. But with the extension of our knowledge of living matter—with the discovery of many of the details of the mechanisms whereby the living cell grows and develops and propagates itself—many other examples of the same kind of thing have come to light. We encounter clear cases of what may be called chemical adaptation—cases in which what is beyond doubt fundamentally the same compound is employed, perhaps in a slightly modified form, for purposes quite different from those for which it was originally intended.

This idea of chemical adaptation we have already touched on in connexion with the building up and use of large molecules. We have seen how the same idea, the synthesis of complicated structures from a small variety of constituent parts by some process of condensation, has been employed in many varied directions with evident success. The proteins afford a striking example of what can be accomplished with limited resources. They are all built up from a score or so of different kinds of amino-acid along with an occasional molecule of sugar or phosphoric acid or some other common compound. They are all variants of the same pattern and yet they are employed for an immense variety of purposes—they are found as merely dead structural material in hair and wool, and as the characteristic and essential compounds of enzymes, the most delicate and important mechanisms of the living cell.

An example or two should suffice to illustrate the type of chemical adaptation which is actually found in plant and animal organisms. To bring out the point it is necessary to refer in some detail to the structural formulae of the substances in question, for it is by means of these formulae that relationships between different compounds are most easily exhibited. As explained in Chapter IV, these formulae are merely

convenient methods of representing the different atoms in any compound and the pattern in which they are arranged. A small modification of structure may make a big difference to the physical appearance and even to the chemical properties of a substance, but inspection of its structural formula will usually at once make clear its real affinities.

To most of us, perhaps, the mention of uric acid stimulates unpleasant associations. It suggests gout, and quite properly so, for gouty patients have deposits of this compound in the joints, especially those of the toes. But uric acid is not always or even usually associated with gout. Indeed, it is normally present in our blood in small but definite amounts, whence it is eliminated by the kidneys, about half an ounce being excreted in something less than a month. Sometimes this uric acid separates from solution in the kidneys or in the bladder, and it may then form granules or stones which are often the cause of severe pain if they are not removed.

If we turn to the physiology of birds and reptiles we find that uric acid performs a really useful function in these animals and is not present merely as a possible cause of pain and disease. In mammals the nitrogen derived from proteins which have been broken down in the course of tissue metabolism is mainly eliminated as urea, which is highly appropriate for the purpose, since it is almost half nitrogen, is highly soluble in water, forms practically neutral solutions, and at ordinary concentrations is quite innocuous to living tissues.

In birds and reptiles, however, uric acid takes the place of urea. At first sight this seems a very much less convenient vehicle for nitrogen excretion, since only one-third of its weight is nitrogen and it is relatively insoluble in water. It happens, however, that the anatomy of birds and reptiles is such that it is not convenient for them to excrete their urine in a liquid form. They concentrate it by reabsorbing water, a process which occurs to some extent in the kidneys even of mammals, but which is carried much further in the uric acid excreting

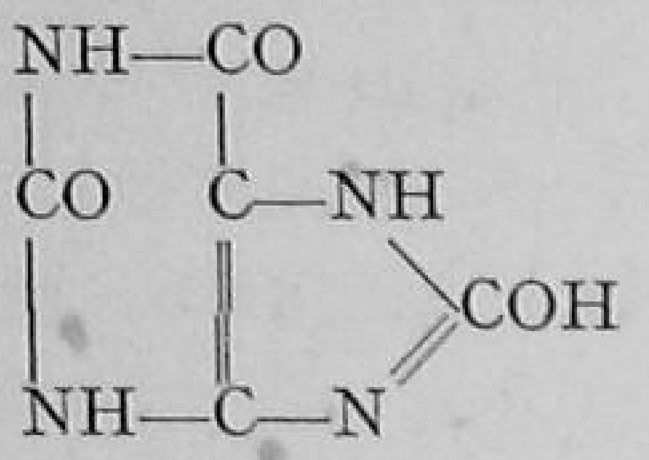
animals. Now to effect concentration of a soluble substance involves the expenditure of energy—the process of squeezing together the dissolved molecules is not unlike that of compressing a gas, and it becomes more and more difficult as the concentration increases. But if the compound is insoluble, like uric acid, it separates spontaneously from solution as the water is removed. The bulk of the water in which the uric acid is dissolved can thus be abstracted relatively easily, just because the uric acid is so insoluble. For animals with a dry or desert habitat this special power to conserve water easily would clearly be a great advantage. Perhaps the early reptiles were adapted to such conditions—the birds, as we know, are descended from specialized reptiles.

Thus far we have met with uric acid as an excretory product, a mere rag-cart for the convenient removal of worn-out goods. If this were all, uric acid would not be a very interesting substance. But to recognize its true significance in nature, it is necessary to regard it as one member of a wide group of substances. Some of these are just as familiar as uric acid itself, or even more so.

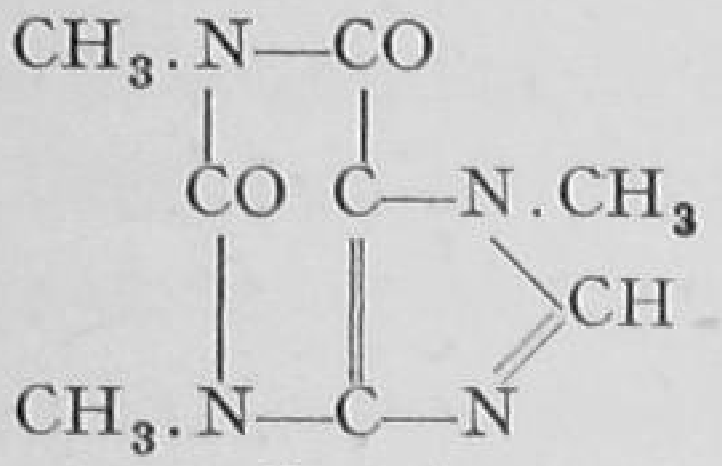
Tea, the cup that cheers, exerts its stimulant effect in virtue of a special compound present in the tea-leaf and extracted from it during the infusion. This substance is also present in the coffee-bean and to some extent in cocoa. It is called caffeine (or theine) and contains the same basic pattern of two "rings" as uric acid; the relationship between the two substances is brought out by the formulae in Fig. 58. A closely related compound, theobromine, is also represented in the figure. This is found in the cocoa-bean and certain other seeds.

It will be seen that the same two rings of carbon and nitrogen atoms are present in all these compounds and that they differ only in respect of the atoms or groups of atoms attached to this special ring structure. They are all modifications of the same fundamental pattern, and as it is sometimes convenient to refer to them collectively, they have been called the "purines".

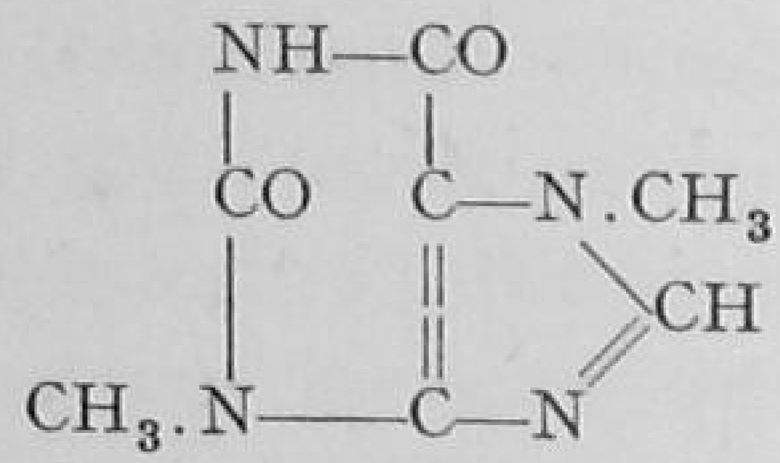
In a very real sense, of course, these purines are drugs—they have a definite action on certain body-cells and tissues and they are consumed, whether as tea or coffee or in bottles dispensed by the chemist—as they sometimes are—primarily in order to produce that physiological effect. They are drugs just as veronal and morphine and cocaine are drugs. But they are mild drugs and produce an effect which is often beneficial and rarely if ever really harmful to the taker. Few will deny



Uric acid.



Caffeine.



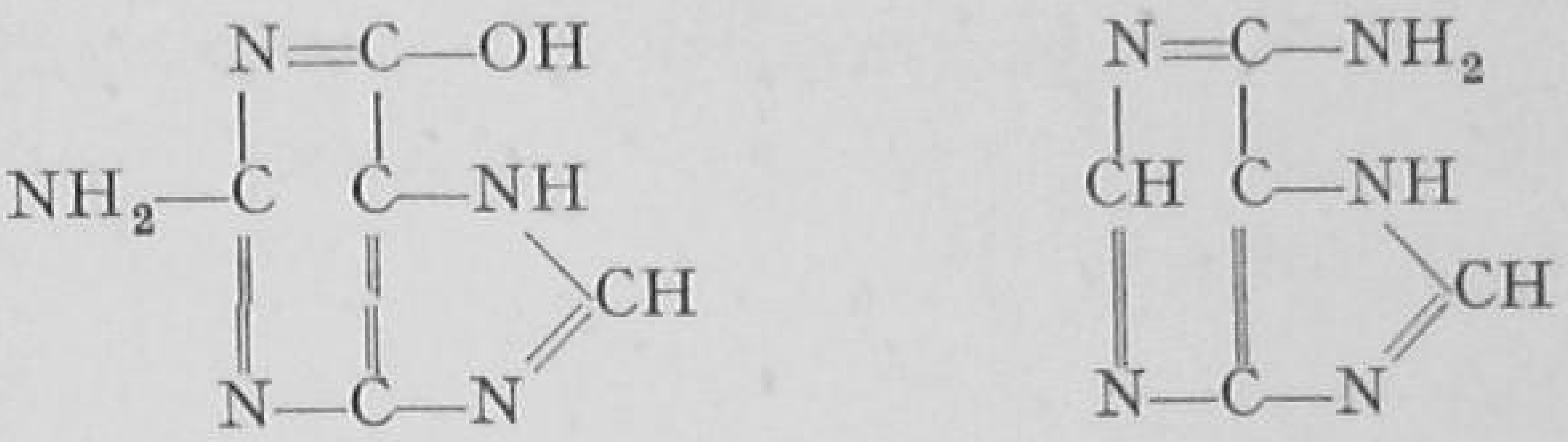
Theobromine.

FIG. 58.

that the introduction of tea and coffee into Europe has enriched the personal and social life of the community. Perhaps one of the secondary results of the development of organic chemistry will be the extension of our resources in the way of mild, beneficent and fool-proof drugs, and the elaboration of the art of drug-taking so as to give real enrichment to life, in the mental as well as in the physical sphere.

The significance of the purines, however, is not limited to the tea-table or the coffee-house, or even the medicine chest; their real importance is to be found on a much more fundamental plane, and indeed these compounds prove to be intimately concerned in the cardinal processes of living matter. It is perhaps significant that cell nuclei are especially rich in their content of purines. From these nuclei may be obtained a substance called nucleic acid, which proves to possess a

somewhat complicated structure built up out of phosphoric acid, sugar, and certain nitrogenous substances. Here we are concerned only with the last-named. They fall into two classes: one class is found to consist of typical purines, of which adenine and guanine are examples. These, like the other

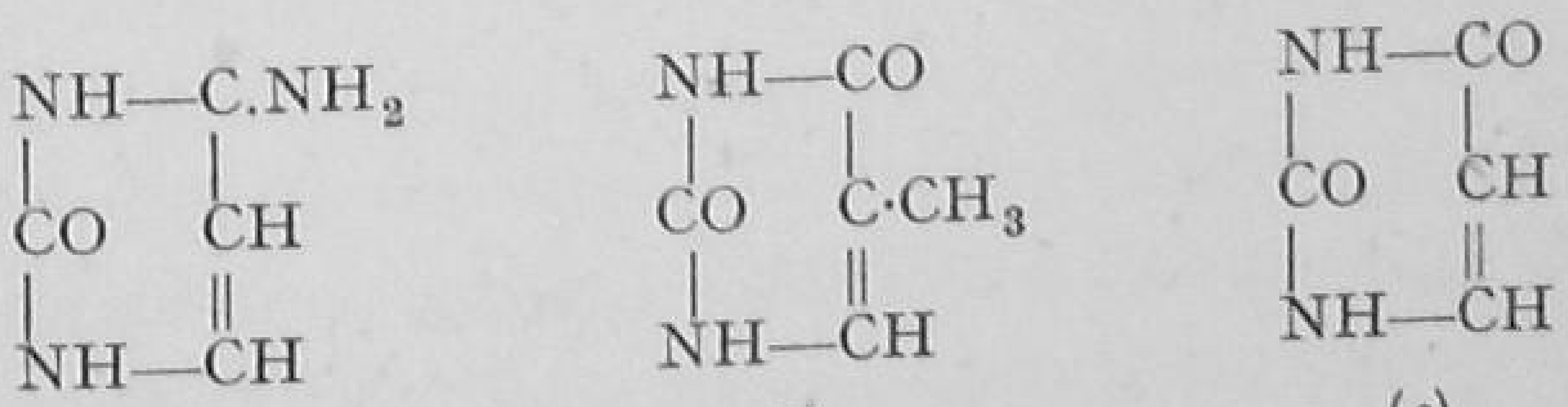


Guanine. Adenine.

FIG. 59.

members of the group already mentioned, contain the characteristic "two-ring" system—they differ only in that they carry somewhat different side-groups (Fig. 59). The purines are thus evidently concerned in the most intimate and essential structures of living matter.

The nitrogen-containing compounds of the second class found in nucleic acid, though not purines, are closely related to them. They possess only one ring, but this ring proves to be none else than the larger ring of the purine structure.



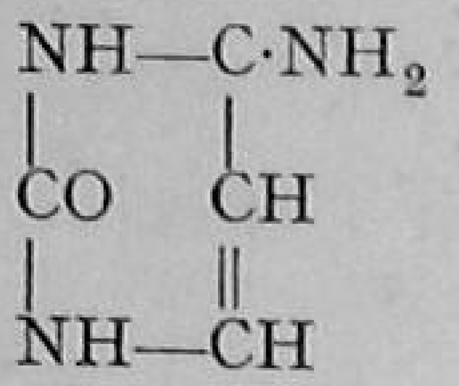
(*a*) Cytosine. (*b*) Thymine. (*c*) Uracil.

FIG. 60.

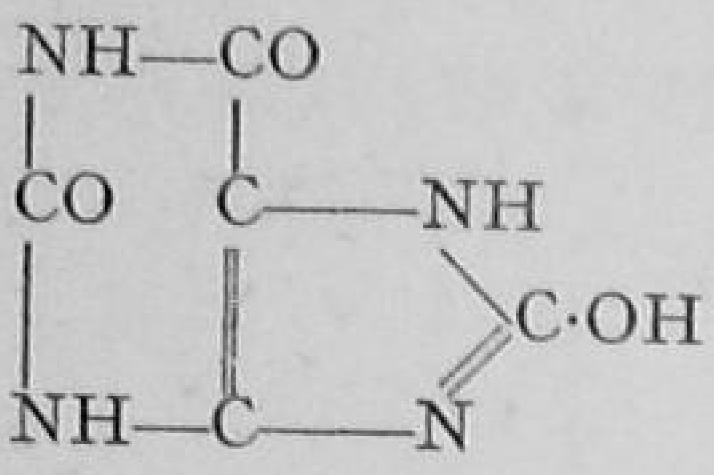
Inspection of the formula of a typical example will make the relationship clear. Fig. 60 (*a*) represents cytosine, and it will be seen that it consists of a six-membered ring containing two nitrogen and four carbon atoms with one or two side-groups attached. Thymine and uracil, Fig. 60 (*b*, *c*), are other common representatives of this class of compounds. We may regard

this "pyrimidine" ring (as it is called) as the basic structure of which the purine two-ring system is a somewhat more complicated variant.

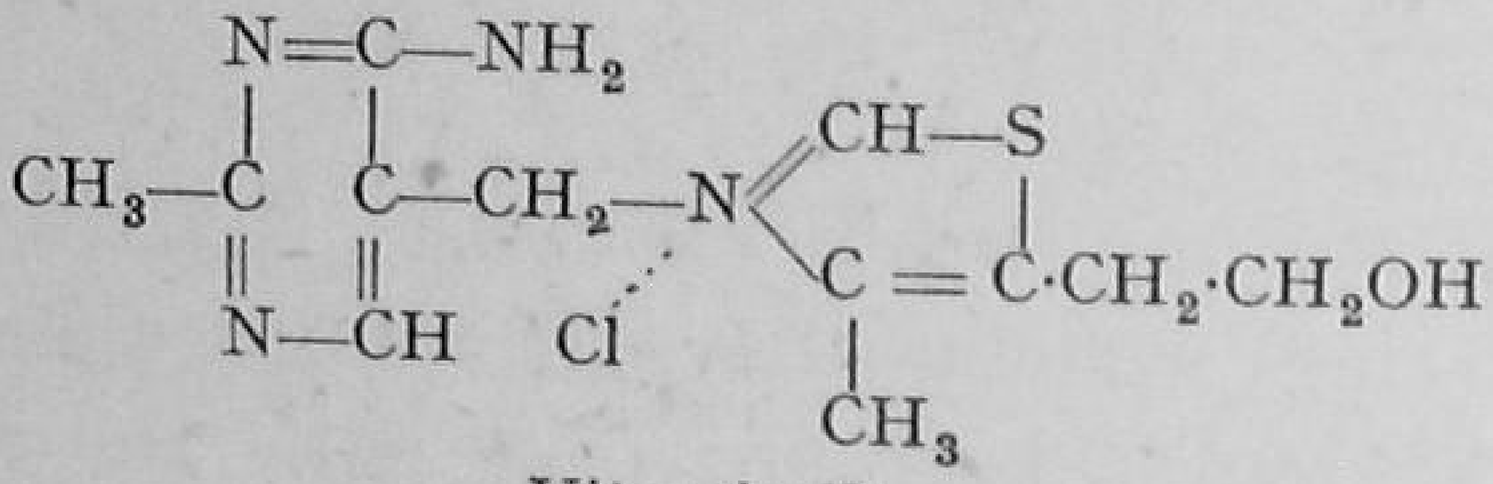
But, what evidence is there that these pyrimidine and purine compounds play any really dynamic, any really vital



Cytosine.



Uric acid.



Vitamin B_1.

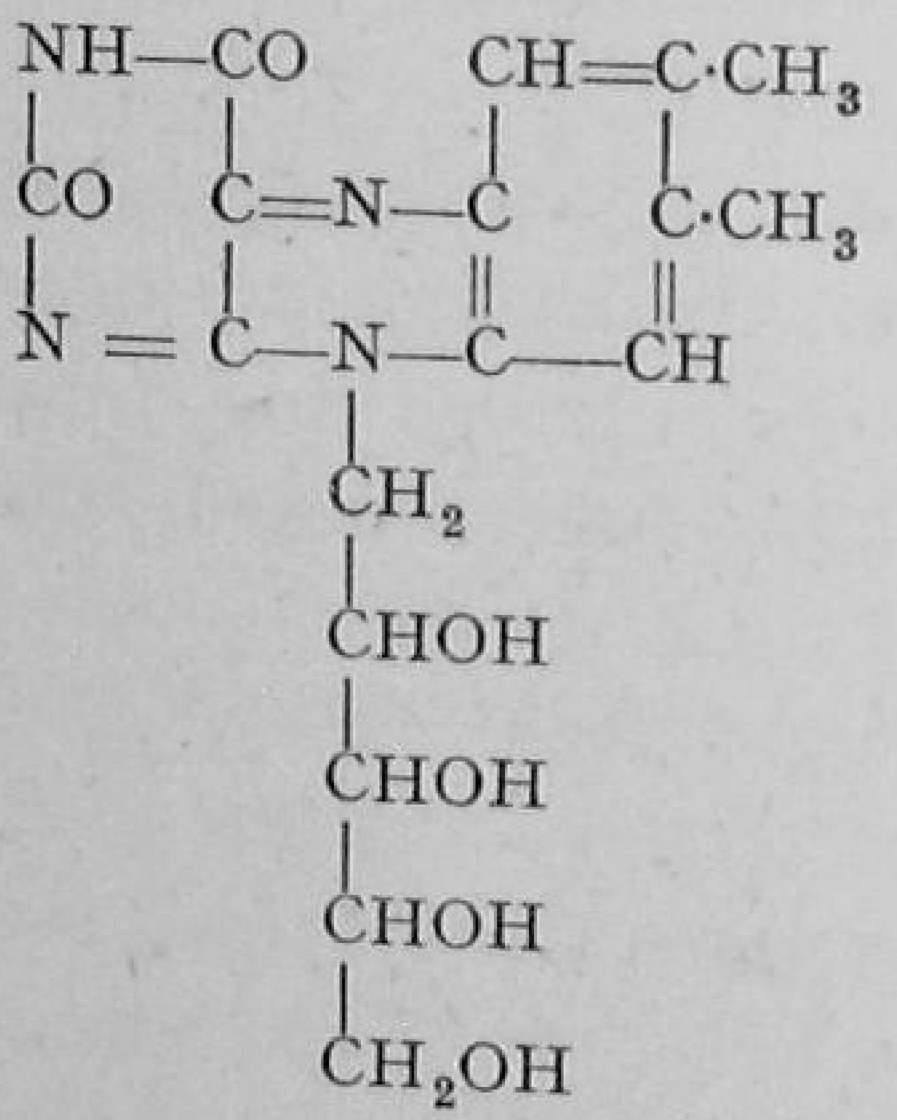


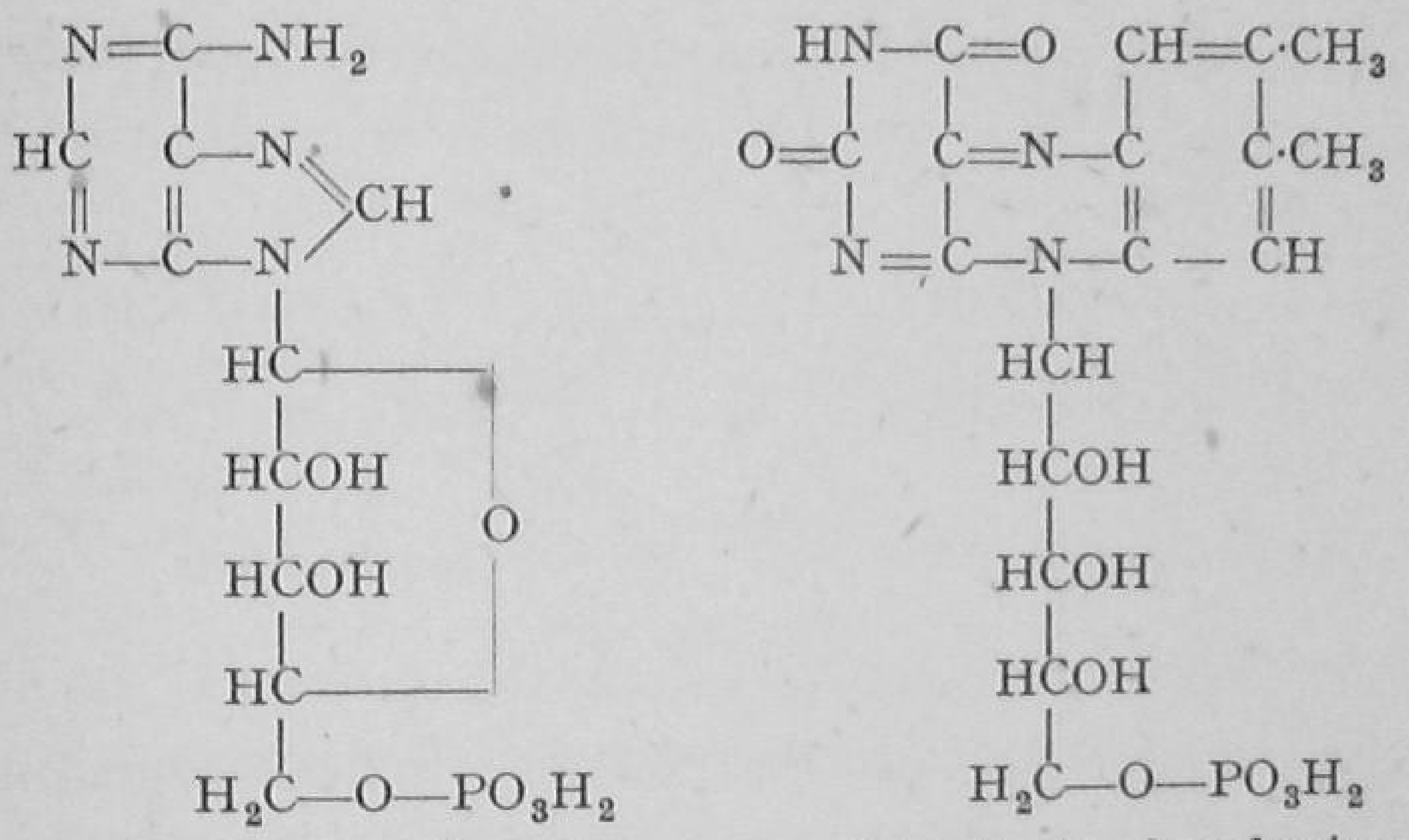
FIG. 61.—Riboflavin.

role in the activity of the cell—as distinct from affording material for mere structural purposes? Before answering this question let us write side by side (Fig. 61) the structures of a purine, a pyrimidine, and those of vitamin B_1 and riboflavin.

It is at once evident that these compounds are closely related to each other: they all contain the characteristic pyrimidine ring of two nitrogen and four carbon atoms. These

vitamins, which are certainly concerned with the dynamics and not the structure of the cell, may both be regarded as somewhat elaborate pyrimidine derivatives just like uric acid and the other purines.

The reader will remember that there is in muscle a compound familiarly called A.T.P., which occupies a key position in muscle chemistry. It is a compound of phosphoric acid and



Muscle adenylic acid. Riboflavin phosphoric acid.

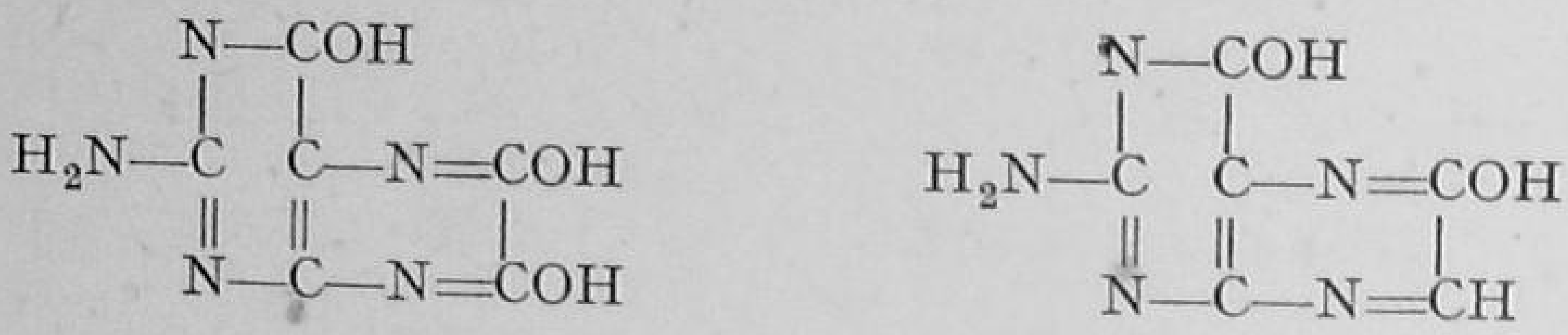
FIG. 62.

adenylic acid; this latter functions as a co-enzyme in various reactions. The name itself suggests a relationship to adenine: an examination of the formula (Fig. 62) will show precisely what the relation is. Not only is it a purine, but, curiously enough, its general architecture is very like that of riboflavin-phosphoric acid (Fig. 62) already encountered as a hydrogen-transporting co-enzyme. In both compounds the nitrogenous part is combined both with a sugar (ribose) and with phosphoric acid. When it is further remembered that the two important cell constituents co-dehydrogenase (I) and (II) also contain adenine it becomes quite clear that the purine structure must have some property rendering it peculiarly appropriate for the construction of co-enzymes.

This seems to be an appropriate place to introduce another class of pyrimidine derivatives, the exact nature of which was

for long obscure, though they have recently turned out to be close cousins indeed to uric acid.

It was between 1889 and 1895 that Gowland Hopkins, afterwards to become world-famous for his pioneer work on the vitamins (Chapter XII), first isolated the pigment from the wings of the Cabbage White butterfly. The compound appeared to be nothing else than ordinary uric acid. It analysed correctly and gave the same reactions, and for many years no one doubted that it was uric acid. In 1926, however,



(*a*) Leucopterin.

(*b*) Xanthopterin.

FIG. 63.

when the German chemists Wieland and Schöpf re-examined the compound they found it very like uric acid, but not quite the same. They showed that in reality it was a new compound and that Hopkins had been misled by very deceptive appearances. His mistake was one which it would have been very difficult for any chemist to avoid in those early days. The striking fact is that Hopkins managed to isolate the substance in a pure crystalline form and to characterize it as precisely as he did. Wieland and Schöpf thought at first that the pigment was formed in some simple way out of two molecules of uric acid, but more recently it has been shown that the molecule is rather simpler than this. It has the structure of Fig. 63 (*a*), differing from uric acid in containing one extra carbon atom in the second ring.

This pigment of the Cabbage White is not the only representative of its type in nature; it is an example of a group of compounds called "pterins" which are widely distributed in the animal and especially the insect world. Thus, for example, a related yellow pigment called "xanthopterin" (the Cabbage

White compound was named "leucopterin") has been obtained from the wings of the Lemon Butterfly. Xanthopterin is simply leucopterin which has lost an oxygen atom (Fig. 63 (*b*)). Xanthopterin has also been found to be the yellow pigment responsible for the decoration on the bodies of wasps.

But recent work has shown that pterins have functions other than the decoration of insects. Xanthopterin or something very like it has been detected in the retina of the dog-fish. Pterins seem, too, to have to do with the manufacture of red blood-cells; there is reason to believe that in the disease of

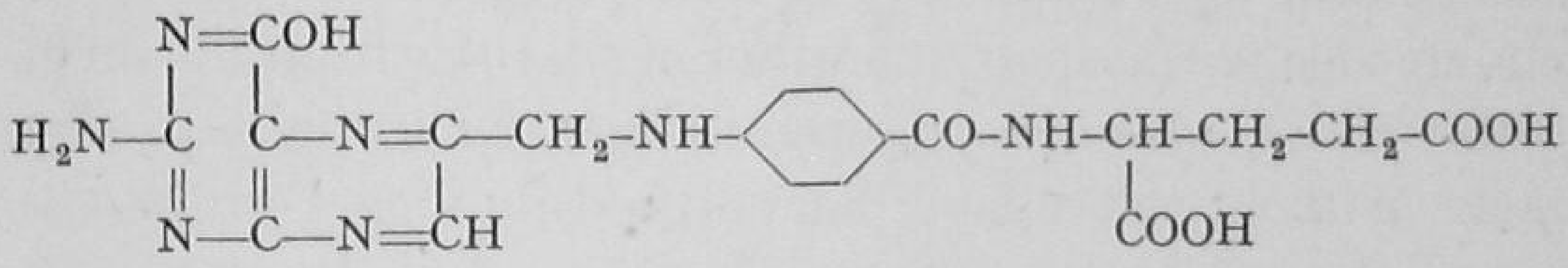


FIG. 64.—Folic acid.

the blood known as pernicious anaemia it is the absence of a pterin derivative that is the cause of the trouble.

A definite connecting link has recently come to light in the form of "folic acid". This name really covers a group of related compounds which were originally detected either as growth factors needed by micro-organisms or as vitamins of the B group. The structure of one representative has recently been elucidated and confirmed by synthesis. It is shown in Fig. 64; the presence of *p*-aminobenzoic acid as an essential component provokes speculation as to the function of this ubiquitous amino-acid in the cell. Folic acid has recently been shown to have value in the treatment of certain types of anaemia. Finally, the reader may have noticed that two of the three rings in riboflavin (Fig. 61) reproduce the characteristic pterin structure, so that this vitamin may be regarded as an elaboration of the pterin theme.

Our second example of the same fundamental structure appearing under many different disguises and being employed for many different purposes, exhibits close analogies to the first. The compounds concerned are to be found in practically

all types of living cells. They serve all kinds of purposes—from carrying out some of the most important functions associated with life to providing pigments of only decorative value, or perhaps of no value at all. The most familiar representatives of this second group of chemical compounds are the red haemoglobin, present in the blood-cells of man and the higher animals, and the green chlorophyll, so abundant as the pigment in the leaves of plants.

Chlorophyll and haemoglobin are both extremely important substances, for as we all know it is in virtue of the power of haemoglobin to combine loosely with oxygen that the blood cells are able to transport quantities of that gas from the lungs to the tissues, where its presence is essential if life is to continue. Without chlorophyll plants could no longer utilize the energy of sunlight for converting carbon dioxide of the air into sugar. Practically all life on earth depends ultimately on this trapping of solar energy through the agency of chlorophyll; for the combustion of foodstuffs in the animal body with the liberation of energy is only the reverse process, and the energy which it yields is really the original solar energy which has been temporarily stored up in the form of somewhat unstable chemical compounds.

Knowing their peculiar properties, we are not surprised that these two compounds, haemoglobin and chlorophyll, prove to be of rather complicated structure, but in recent years much progress has been made towards a complete knowledge of their constitutions. For this we are indebted to many workers, foremost among whom are R. Willstätter, whose pioneering work blazed the trail and opened up this new region, and, more recently, Hans Fischer, whose remarkable synthetic experiments have settled the main points in the structure of chlorophyll and have resulted in a partial synthesis of haemoglobin itself.

From our present point of view the outstanding result of this complicated and difficult field of chemistry is that both chlorophyll and haemoglobin are derived from the same basic

structure. This basic skeleton, which has been called the "porphin" nucleus, is considerably more complicated than the

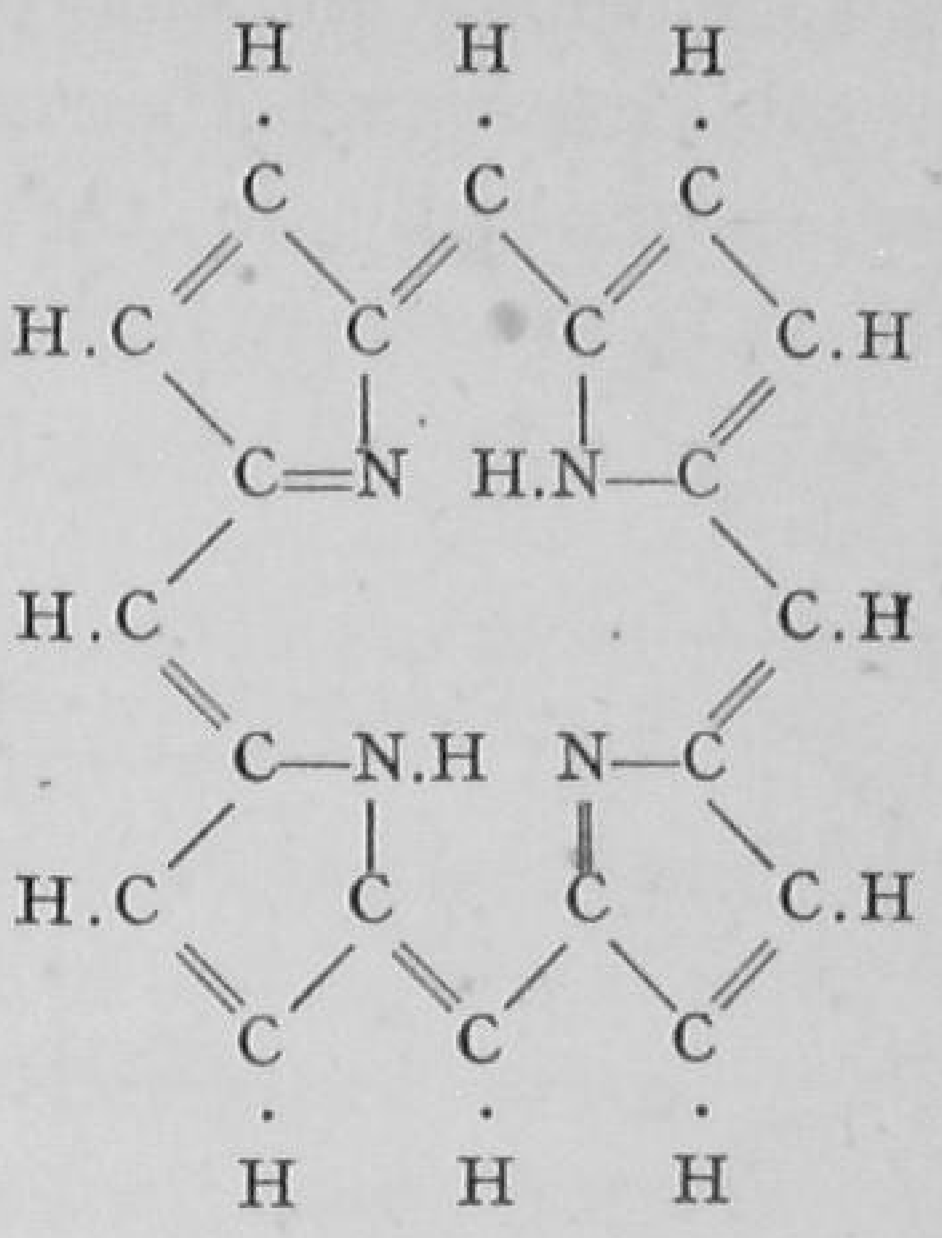


FIG. 65.—Porphin.

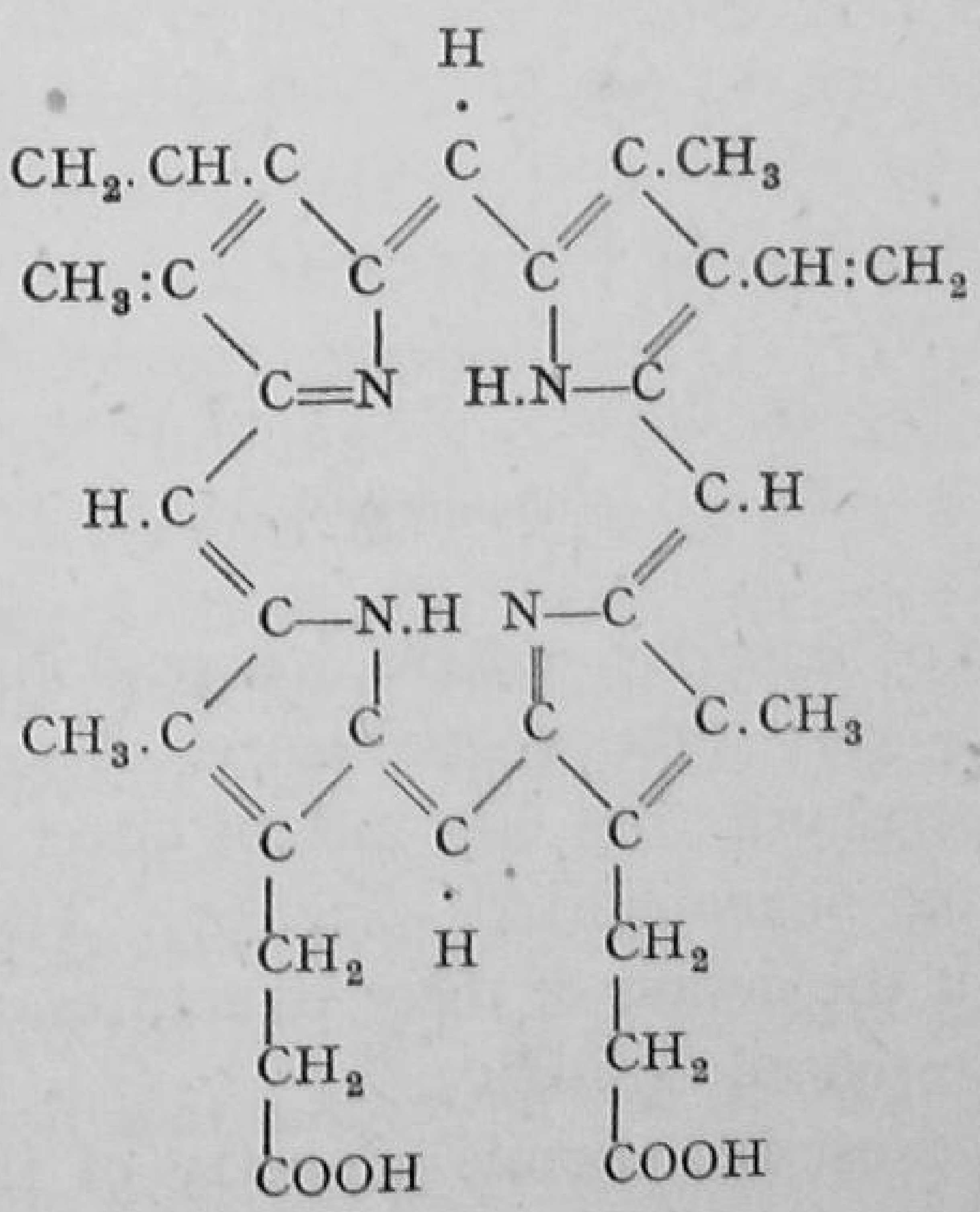


FIG. 66.—Protoporphyrin.

purine system, but in spite of its large size and somewhat elaborate structure it proves to be remarkably stable towards heat and chemical reagents. It is represented in Fig. 65; as will be seen, it contains four rings united together in the form

of one large ring by four =CH— groups, the double bonds being arranged in a characteristic pattern throughout the whole structure. In haemoglobin and chlorophyll, the porphin nuclei carry various side-chains and other modifications; these modifications differ substantially in the two compounds, though not so much as to hide their fundamental similarity.

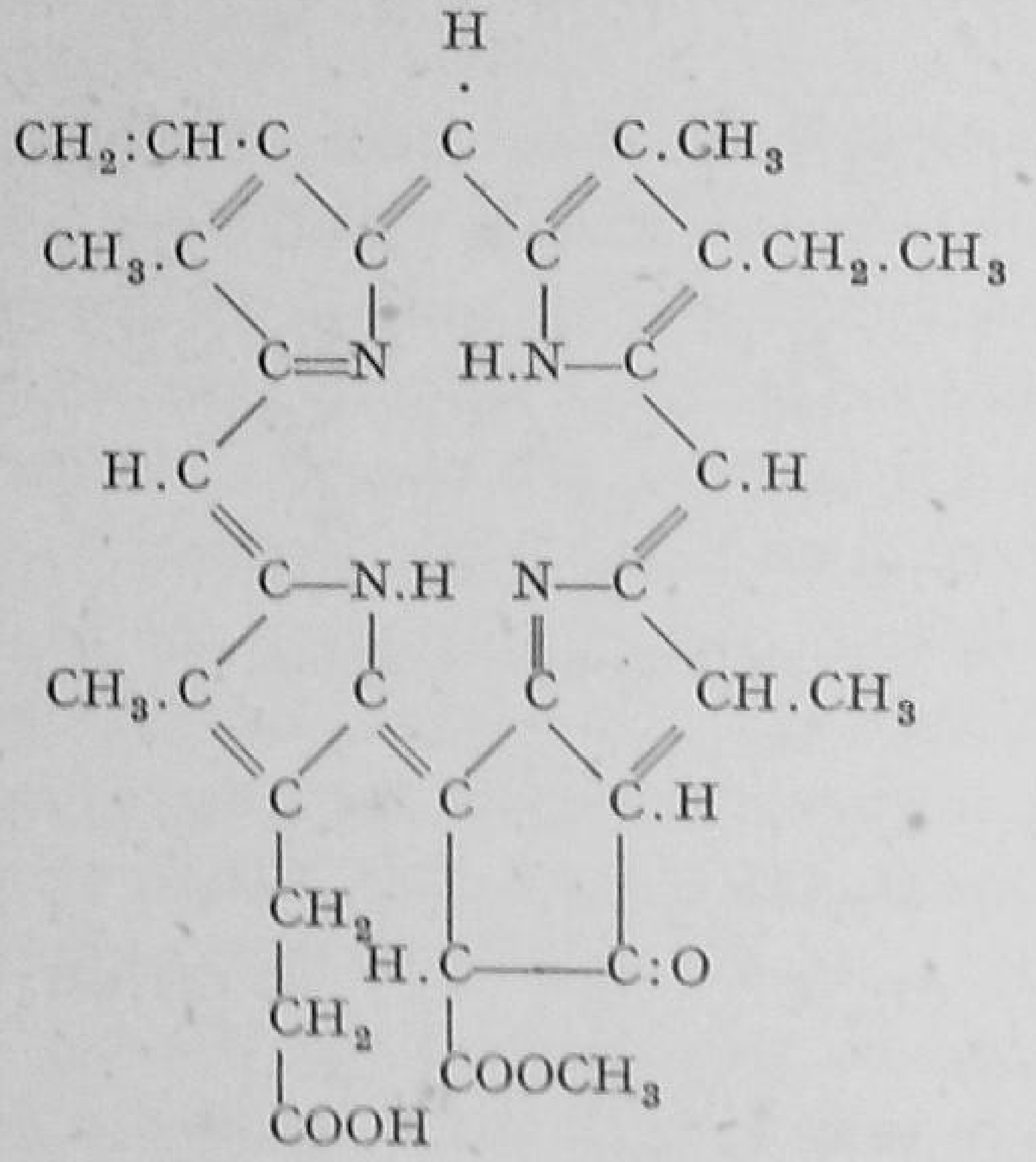


FIG. 67.—Phaeophorbide.

Even in respect of secondary details, haemoglobin and chlorophyll exhibit a very close resemblance. Thus the former contains protoporphyrin (Fig. 66), and the latter the somewhat more complicated phaeophorbide (Fig. 67). The reader need not worry about the details of these structures, it is sufficient to notice their essential similarity.

Perhaps the most remarkable property of these porphins is their power to form relatively stable compounds with many metals. Thus, for example, in haemoglobin the protoporphyrin is combined with iron to yield a very special type of compound called haem; whilst in chlorophyll the metal present is magnesium. The unusual structure of these porphin metal compounds is paralleled by their very peculiar properties. But

even these singular substances require further elaboration in order to develop fully their unique potentialities. The haem is combined with a very special protein called globin—and so the familiar red haemoglobin is produced. In the case of chlorophyll, the magnesium porphyrin complex is united with a somewhat complicated alcohol called phytol. We may represent these relationships schematically as follows:

Protoporphyrin + Iron + Globin → Haemoglobin
Phaeophorbide + Magnesium + Phytol → Chlorophyll

We have seen in our discussion of enzymes that the living cell is in the habit of making use of molecular stepping-stones to facilitate the transfer of atoms from one compound to another. Now we may regard the haemoglobin of the blood as a molecular stepping-stone on a grand scale. Or perhaps we should here think of ferry-boats rather than stepping-stones. The oxygen is transferred to the molecule of haemoglobin in the lungs, it is transported on it along the blood-stream until it reaches the tissues, and there it is unloaded and set free to carry out its necessary function in metabolism. But although this "ferry-boat" function is the natural role of haemoglobin in the body, the chemist has found that it can act as a stepping-stone for oxygen in another way, one much more closely resembling the hydrogen stepping-stones which we met in connexion with enzymes. Indeed, this property belongs not only to haemoglobin, but also to the haem moiety of the molecule by itself, and it is shared by many other porphin-iron compounds. In the presence of substances such as hydrogen peroxide, which contain oxygen in a somewhat loosely bound state, the haem molecule (and many of its derivatives) takes up an oxygen atom. This is, however, readily passed on to any suitable molecule which will receive it. The net result of the process is that hydrogen peroxide has lost an atom of oxygen (and become a molecule of water), while a third compound has taken up the atom, and so become oxidized, the haem derivative having acted merely as an intermediary.

Haemoglobin and haem behave very much as if they were enzymes, promoting the oxidation of many compounds by hydrogen peroxide.

Now there is a true enzyme, found particularly in many plant juices, which also promotes this reaction. The latter, however—it is called peroxidase—differs from haem and haemoglobin in one very important particular: it is inactivated by boiling; haem being a stable compound remains unimpaired in its efficiency after such treatment, whilst haemoglobin, though altered by heat, still remains quite active, since the important iron-porphin system rests intact.

This special power of haemoglobin and haem to promote oxidations by hydrogen peroxide forms the basis of a test for blood which is of great importance for both clinical and medico-legal purposes. The test can be made a very delicate one, for we can choose as the substance to be oxidized one which, though practically colourless to begin with, is converted by oxidation with hydrogen peroxide in the presence of blood or haemoglobin derivatives into an intensely coloured substance, so that a minute amount of oxidation may be detected. When one remembers that the haemoglobin acts merely as a stepping-stone for the oxygen, so that one molecule of it may account for the oxidation of hundreds or perhaps thousands of molecules of the third compound, it is easy to understand that the test is a very delicate one. Furthermore, it is given by bloodstains even though they are old and apparently decomposed, for the important stable haem complex remains intact. The possible interference of the enzyme peroxidase may be eliminated by boiling the suspected material so as to inactivate the enzyme, should it be present.

Man, then, has seized on the special chemical properties of haem and its derivatives and used them for his own purposes —as the basis of tests for the detection of diseases and the exposure of crime. But nature had long anticipated him in realizing the wide potentialities of these compounds and the possibility of adapting them to many purposes. For they are

found not only in the red blood cells as haemoglobin, but also in practically every living cell, under a somewhat different guise. And in this form, though they are present in only very minute amount, they play an indispensable part in the processes of life. They act as stepping-stones transporting oxygen from one compound to another just as in the pathologist's test for blood. In the cells they form one of a whole series of stepping-stones, one of the many small stages by which oxygen is utilized in the tissues. The haem derivatives in question are called cytochromes (see p. 117); there are usually several kinds even in the one cell, but in quantities so small that they can be conveniently observed, and the changes which they undergo followed, only by means of the spectroscope. In heart muscle there is present only perhaps about one part of cytochrome in 3,000 parts of tissue. The poisoning effect of hydrogen cyanide (prussic acid) is largely due to its power to put these cytochromes out of action—a fact which explains why so little of this poison may prove lethal, and is at the same time convincing proof of the importance of these haem derivatives in the living body.

Extracts of many animal and vegetable tissues when added to a solution of hydrogen peroxide cause an immediate effervescence. This is because they contain an enzyme, catalase, under the influence of which hydrogen peroxide decomposes with the formation of water and oxygen. The latter, being but very slightly soluble in water, separates as a gas, and so causes the effervescence. This very common enzyme catalase, which probably acts as a biological "scavenger" preventing the accumulation of the poisonous hydrogen peroxide, has been separated from the inactive material which accompanies it in the crude cell extracts, and was finally crystallized. It was found to belong to our porphin group of substances; like haemoglobin, it consists of the iron porphin compound haem united to a protein, only here the protein is not globin but another, appropriate to the development of the function which the complete enzyme performs. This association of the active

group with a special protein reminds us of the similar case of the yellow oxidation pigment: we may imagine the protein to act as a kind of hand-rail to help the oxygen atoms to reach the haem molecules from the hydrogen peroxide whence they start. It is now generally agreed that the structure of peroxidase, which we referred to above, is somewhat similar—an iron-containing haem component in association with a specific protein. As we have seen, compounds of the haem type have in general a peroxidase activity—that is to say, the power of promoting the oxidizing action of hydrogen peroxide—in no mean degree, but the association of haem with the specific protein results in the enhancement of this activity. This increase in activity is so great that when the protein is altered by heating (that is, denatured) there is a great reduction in activity. For all practical purposes these peroxidase solutions are completely inactivated by heat, even though the haem itself is not destroyed. The hand-rail makes all the difference —the stepping-stone is almost entirely useless by itself.

In any machine highly active components are apt to wear out, and these haem compounds in the tissues form no exception. Sometimes, no doubt, the damage to the molecule can be repaired—in any case, the iron can be recovered and used again—but a certain amount of waste material accumulates and must be eliminated. This waste material, of course, consists of the iron-free residue of the haem molecule in a more or less degraded condition. In other words, the products in question consist of the protoporphyrin referred to above (see p. 275), somewhat the worse for wear. If the side-chains only are affected the products still contain the porphin nucleus and are classified as porphyrins.

But the wearing out of the haem molecule may go further; the characteristic porphyrin ring may be broken at one point. In this way are formed substances more familiar to most of us than the porphyrins, for we all know the sickly colour of bile and the greenish-yellow hue which is so characteristic of people suffering from jaundice. The bile pigments are, in fact,

broken-down remnants of haemoglobin which are being eliminated from the body by the liver. The relation between protoporphyrin, the porphin component of haemoglobin, and bilirubin, the commonest bile pigment, can be seen by comparing Figs. 66 and 68.

For most of us the bile pigments may have unpleasant associations with disease, for if the function of the liver is impaired, either through damage or as the result of obstruction

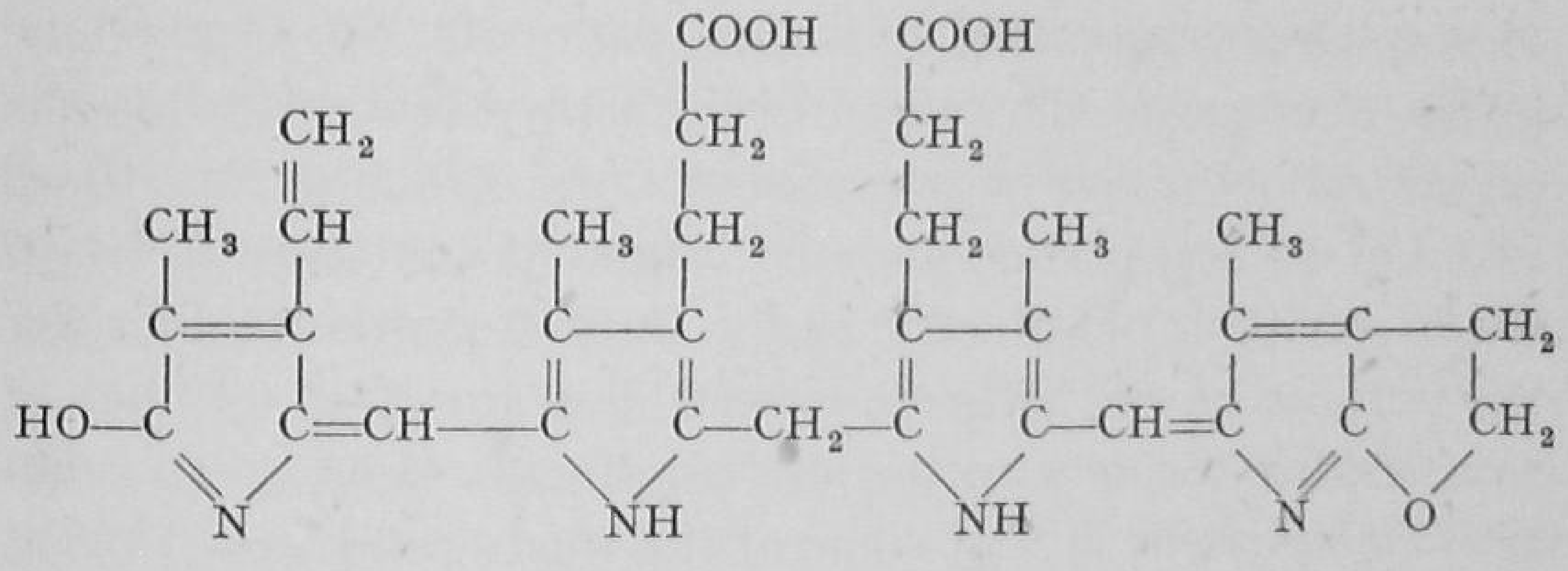


FIG. 68.—Bilirubin.

of the bile duct, it may fail to eliminate these waste products, and the consequent accumulation of the pigments in the tissues accounts for the development of jaundice. A similar pigmentation of the blood and tissues may result not from the failure of the liver to act efficiently, but from an over-production of the pigments themselves—a condition which often accompanies diseases of the blood. The imperfect or damaged blood cells (like worn-out ones in normal people) are dealt with by the liver; many of them are broken up and much of their haemoglobin decomposed, with the formation of excessive amounts of bile pigments. This second type of jaundice is quite different from the first; but in both cases the bile pigments are innocuous in themselves; the pigmentation is a superficial sign of the disease, not its cause nor even an important symptom.

But nature would be lacking in resource if she could not find a use for by-products relatively so abundant as porphyrins

and bile pigments. It is in the bird world chiefly that we find them being utilized, for decorative purposes. In the egg-shells of the gull and certain other birds there occurs a bluish-green bile pigment called "oocyan" (closely related to or identical with the "utero-verdin" found in dog's placenta). The reddish tints of the shells of many birds' eggs are due to the presence of protoporphyrin (Fig. 66), which has actually been separated from the eggs of sparrows, cuckoos, finches, larks, plovers, gulls, and a few less familiar birds. Some birds also make use of porphyrin compounds as feather pigments: the bright blue in the plumage of the turaco bird has been identified as the copper salt of uroporphyrin, a compound which is sometimes found in urine in certain diseases. Man has contrived to adapt the by-products of industry, in the form of synthetic dyes, for the purpose of aesthetic expression, but scores of millions of years earlier the same principle had already been given practical embodiment in that some of the waste products of blood and tissue were employed by birds as pigments in their efforts at artistic display.

Before leaving this group of substances a brief reference may be made to some recent work of rather unusual interest. For long it has been a matter of controversy amongst geologists and mining engineers as to whether the oil deposits from which we derive our petrol are of animal or vegetable origin. Now it has been found possible to isolate porphyrins from coal, shales, oil, and similar carbonaceous deposits, and the identification of these porphyrins gives the answer to this vexed question. For porphyrins derived from the chlorophyll of plants—the reader will remember that phaephorbide, the characteristic structure present in chlorophyll, is, like haemin, a porphin derivative—are different in certain minor details from those of animal origin. Now by far the greater part of the porphyrins present in these geological deposits proved to belong to this chlorophyll group, so it may be concluded that our shales and mineral oils are principally of vegetable origin. Thus the development of the pure chemistry of this

complicated and ubiquitous group of substances has borne fruit in a very unexpected quarter.

And now for our third group of compounds illustrating the ability of the same chemical structure to appear in a variety of disguises, and so perform a number of different functions. This group is of astonishing ubiquity.

Gallstones, sex hormones, bile salts and digestion, vitamin D and rickets, alkaloids from plants of the potato family, the principles present in digitalis and other drugs which act on the heart, the peculiar poisons in the skin of certain toads, and finally cancer—these are the subjects which are strung together on this chemical thread. An adequate discussion of this group of substances would itself take many chapters and lead us into highly complicated organic chemistry. But the main point can be brought out fairly readily, especially as we are already familiar with some of the more important members of the group.

Let us begin with cholesterol, for this is perhaps the most easily accessible compound in the group. This substance is present in most animal tissue, where it probably exists as an integral part of the physical structure of the cell; but it is obtained most easily from gallstones, for these usually consist of almost pure cholesterol, somewhat discoloured by bile pigments. Cholesterol is a normal constituent of bile, and the occurrence of gallstone is due to the failure of the compound to remain in solution, the result of some obscure disturbance of a rather unstable equilibrium. Now cholesterol is but one of a large group of "sterols", compounds which are found in plant and animal tissues. Cholesterol has the structure shown in Fig. 69, *a*, and it is the ring system which forms the basis of this structure, the "sterol skeleton" (Fig. 69, *b*), which constitutes the common link between the various members of this group.

From this point of view let us examine those members of the group with which we have already become acquainted, namely, the sex hormones and the anti-rachitic vitamin. The

sex hormones prove to be derived very simply from the fundamental skeleton. Formulae are here more eloquent than words.

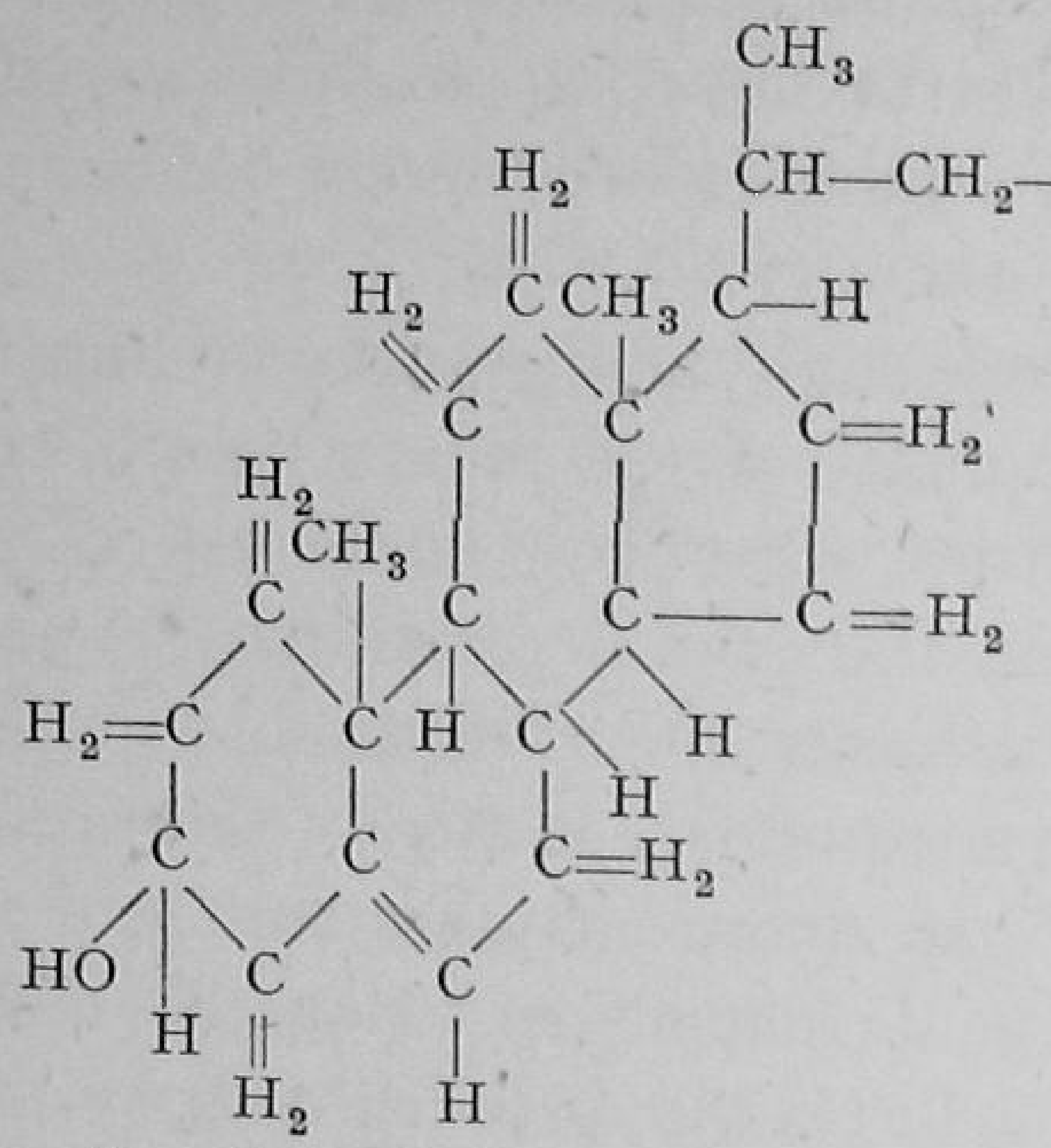


FIG. 69 (*a*).—Cholesterol.

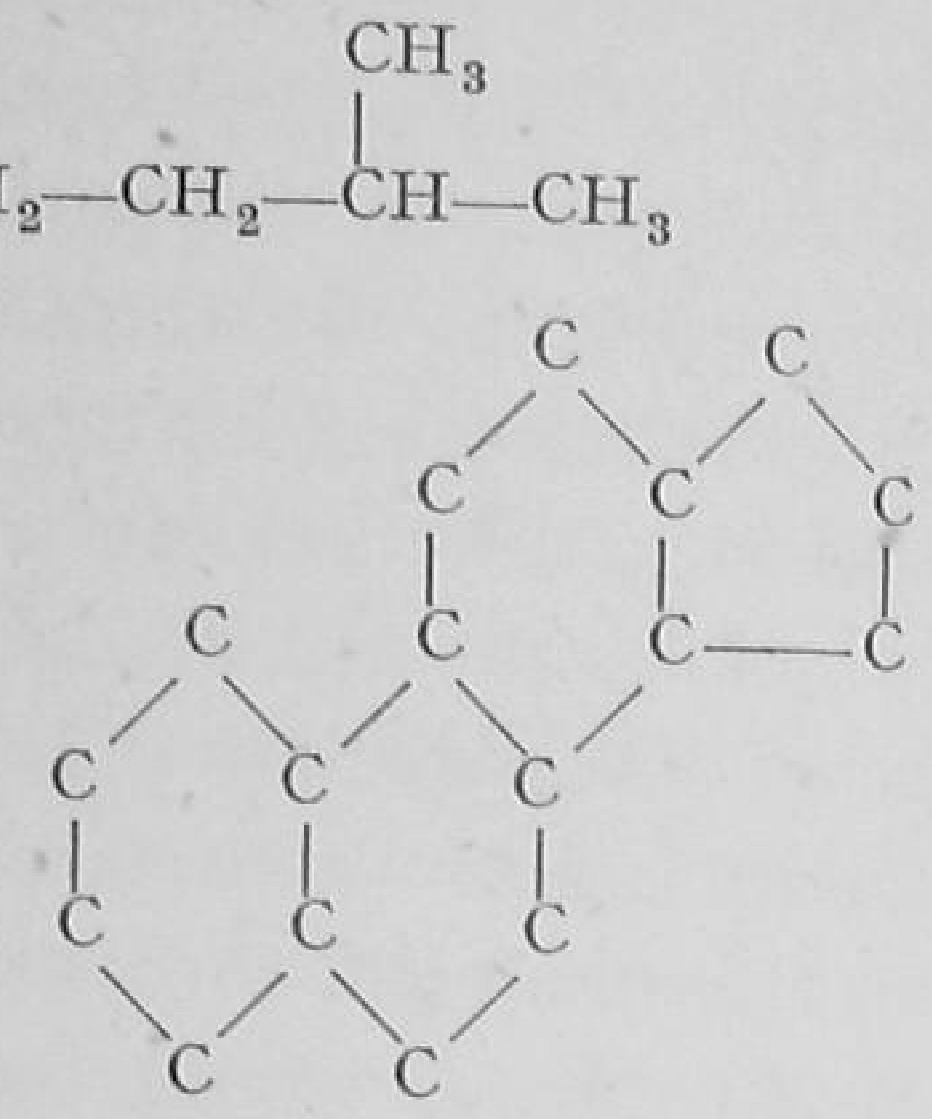
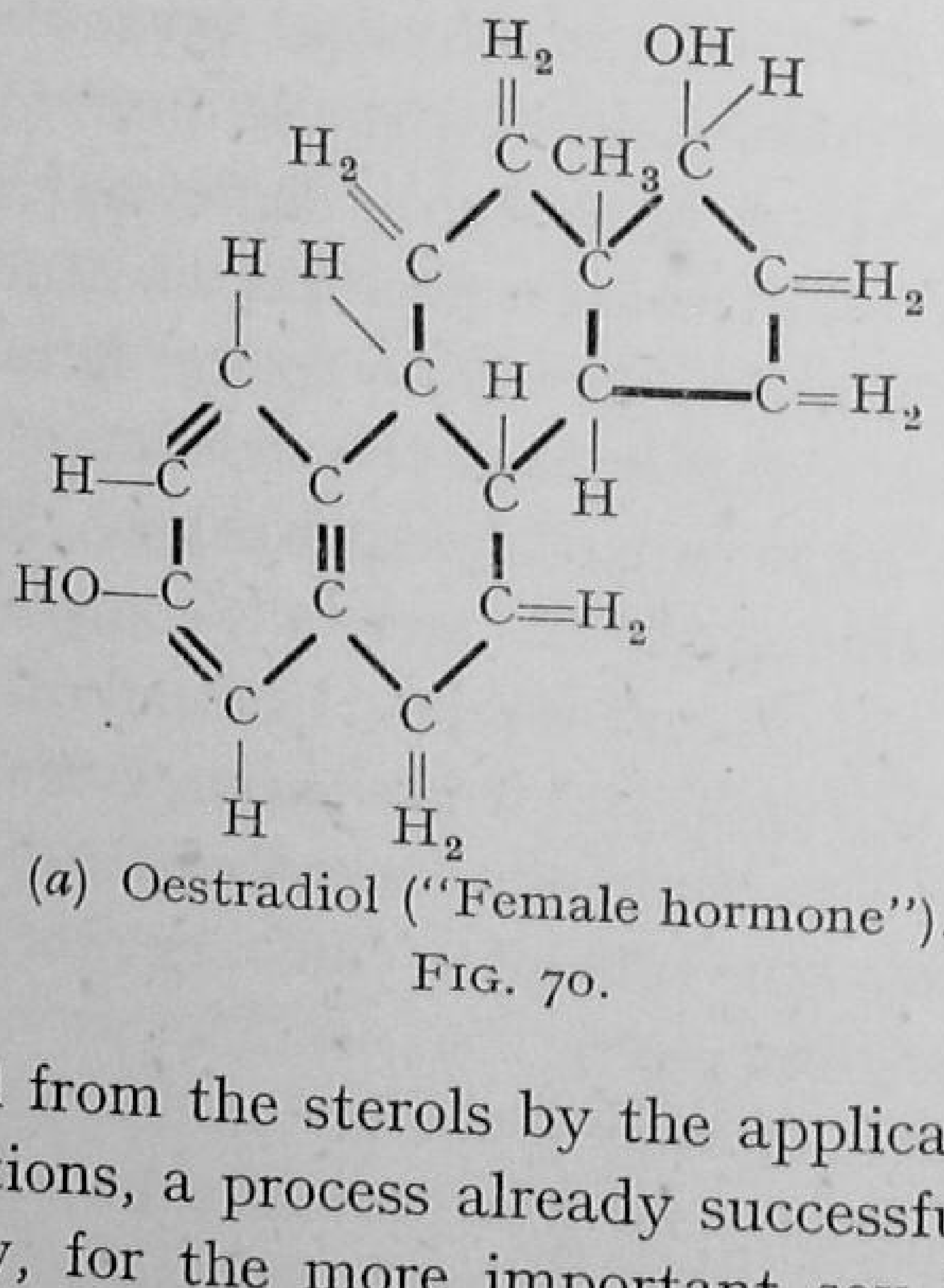


FIG. 69 (*b*).—Sterol skeleton.

Two of the more important of these hormones are represented in Fig. 70; the reader will see that the sterol skeleton is common to them all. There is little doubt that in the body they are

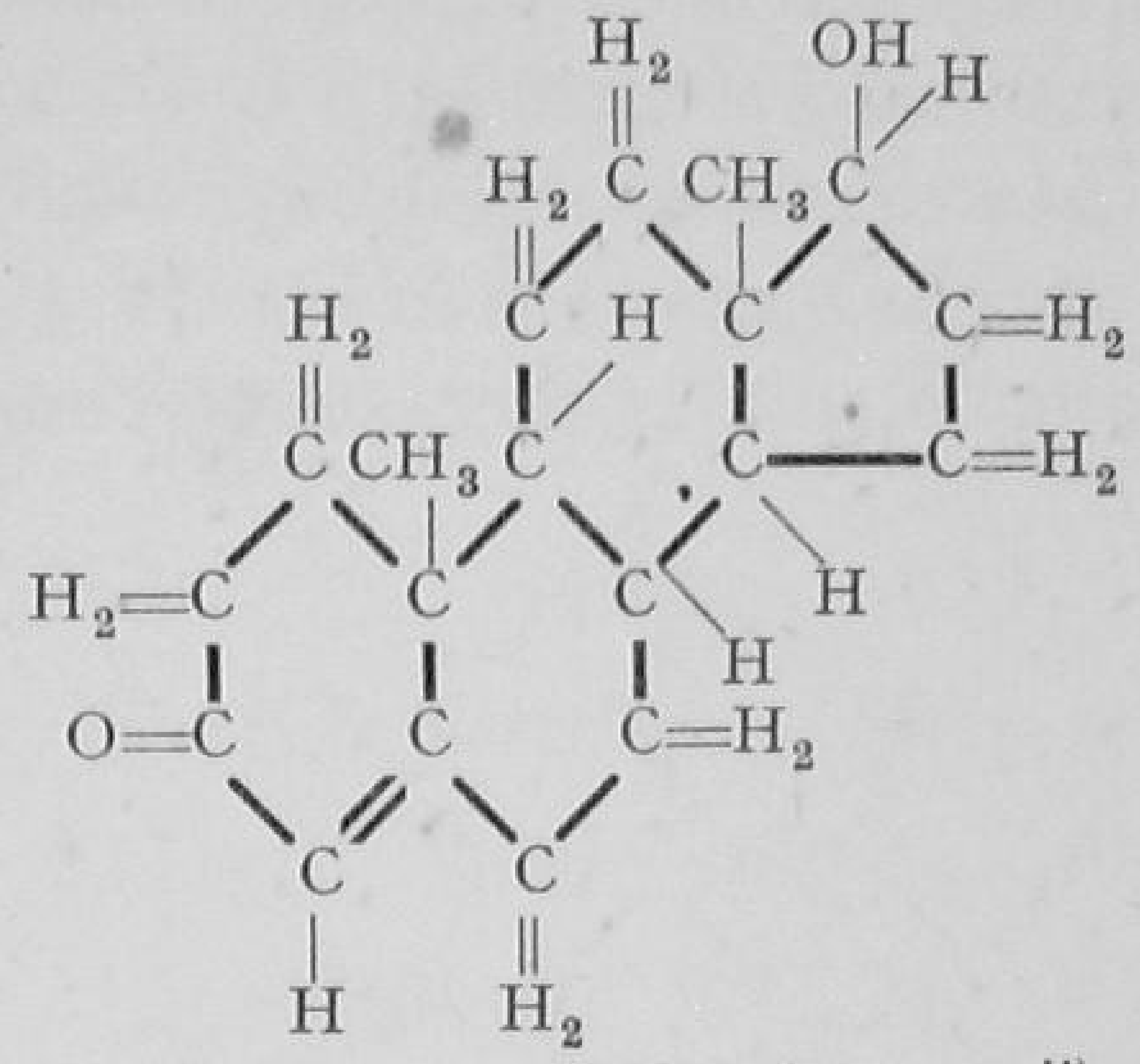


(*a*) Oestradiol ("Female hormone").

FIG. 70.

in fact formed from the sterols by the application of suitable chemical reactions, a process already successfully imitated in the laboratory, for the more important sex hormones have

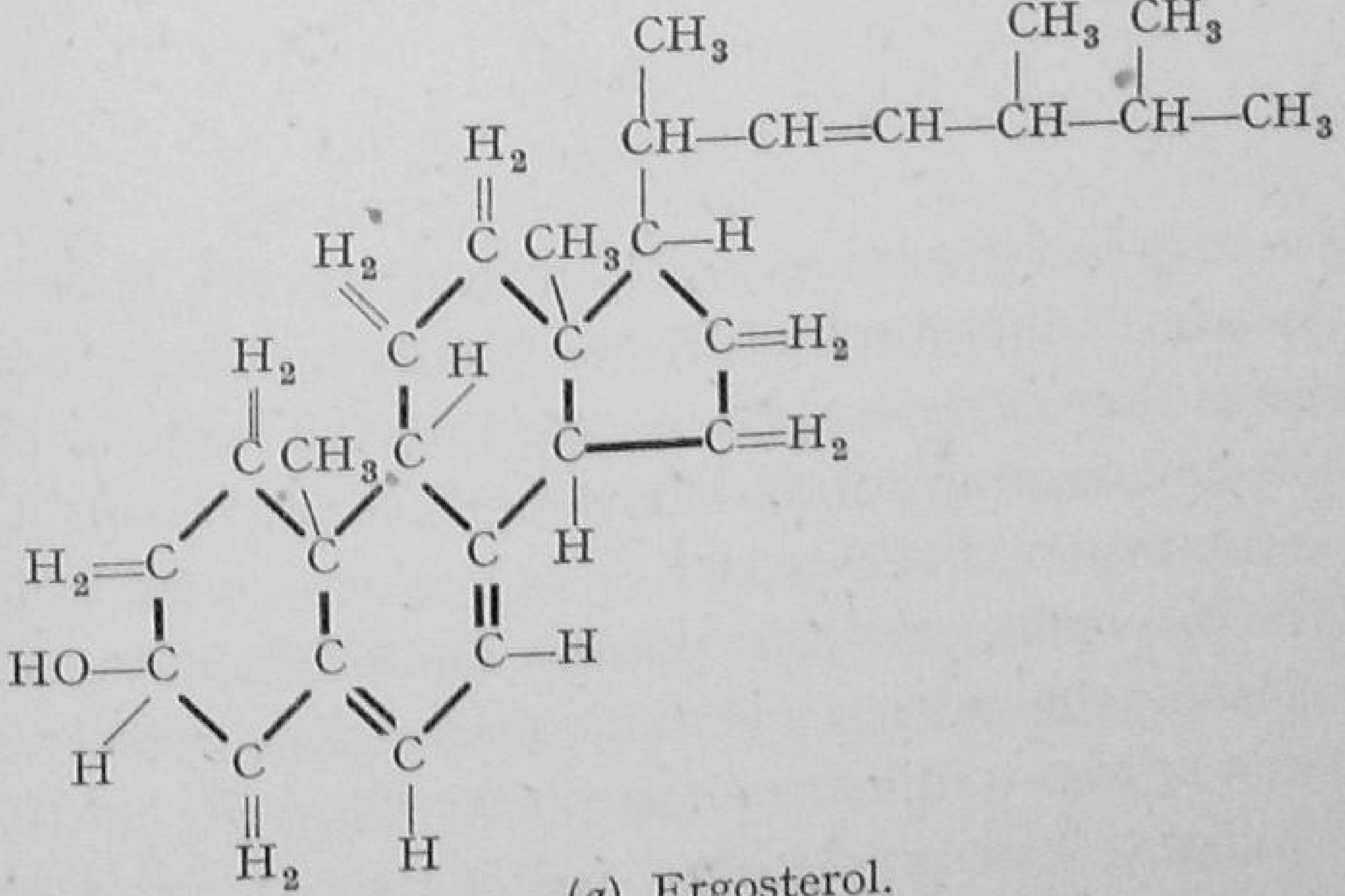
already been prepared by the ordinary methods of organic chemistry from suitable naturally occurring sterols.



(*b*) Testosterone ("Male hormone").

FIG. 70.

The close relation of the anti-rachitic vitamin D to the sterols was evident as soon as it was found that this dietary factor was produced when one of the sterols, ergosterol, was

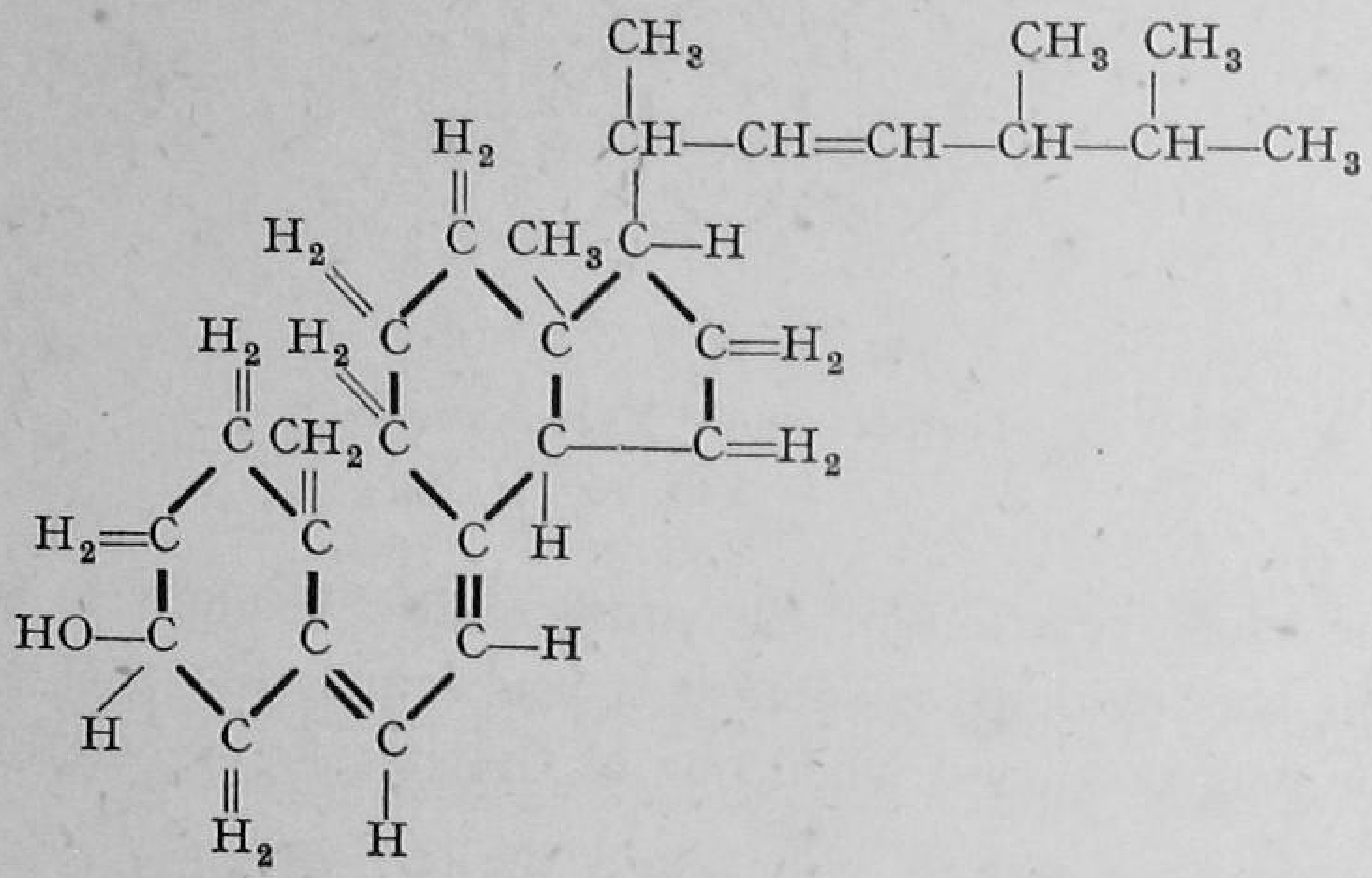


(*a*) Ergosterol.

FIG. 71.

treated with ultra-violet light (p. 195). Ergosterol (Fig. 71, *a*) is closely related to cholesterol—only it has three double bonds instead of one—but the active product formed by irradiation,

calciferol, has no longer the characteristic sterol skeleton. The treatment by the ultra-violet light has resulted in the opening of one of the four rings and in the absence of definite knowledge as to how it was actually prepared the new compound might not be thought to be related to this group of substances at all. However, by writing its formula as in Fig. 71, *b*, the structural connexion is brought out. Other sterols beside ergosterol



(*b*) Calciferol.

FIG. 71.

produce anti-rachitic compounds on irradiation. These other "provitamins" differ from ergosterol only in respect of the side-chains they carry—in every case the ring system remains the same and the transformation brought about by ultra-violet light is the fission of the same ring at the same point.

Of the bile acids, the heart poisons and stimulants, and the toad poisons, the briefest mention must suffice, with perhaps a formula or two to illustrate the point. They all contain the same four-ring structure as the basis of their molecular architecture. The bile acids, for example, of which the salts are secreted by the liver in the bile, exercise a beneficial influence on the absorption of fats and other insoluble substances from the gut. They do this by holding many insoluble substances in a finely divided form or even in solution. These

bile acids, of which there is a whole group, have structures such as that shown in Fig. 72, which represents the common one called cholic acid.

The heart poisons are well-known substances which are used in Europe as drugs to alleviate heart disease and in Africa as arrow poisons to kill tribal enemies. The toad poisons are not so familiar to most of us. The toad stores them in his skin,

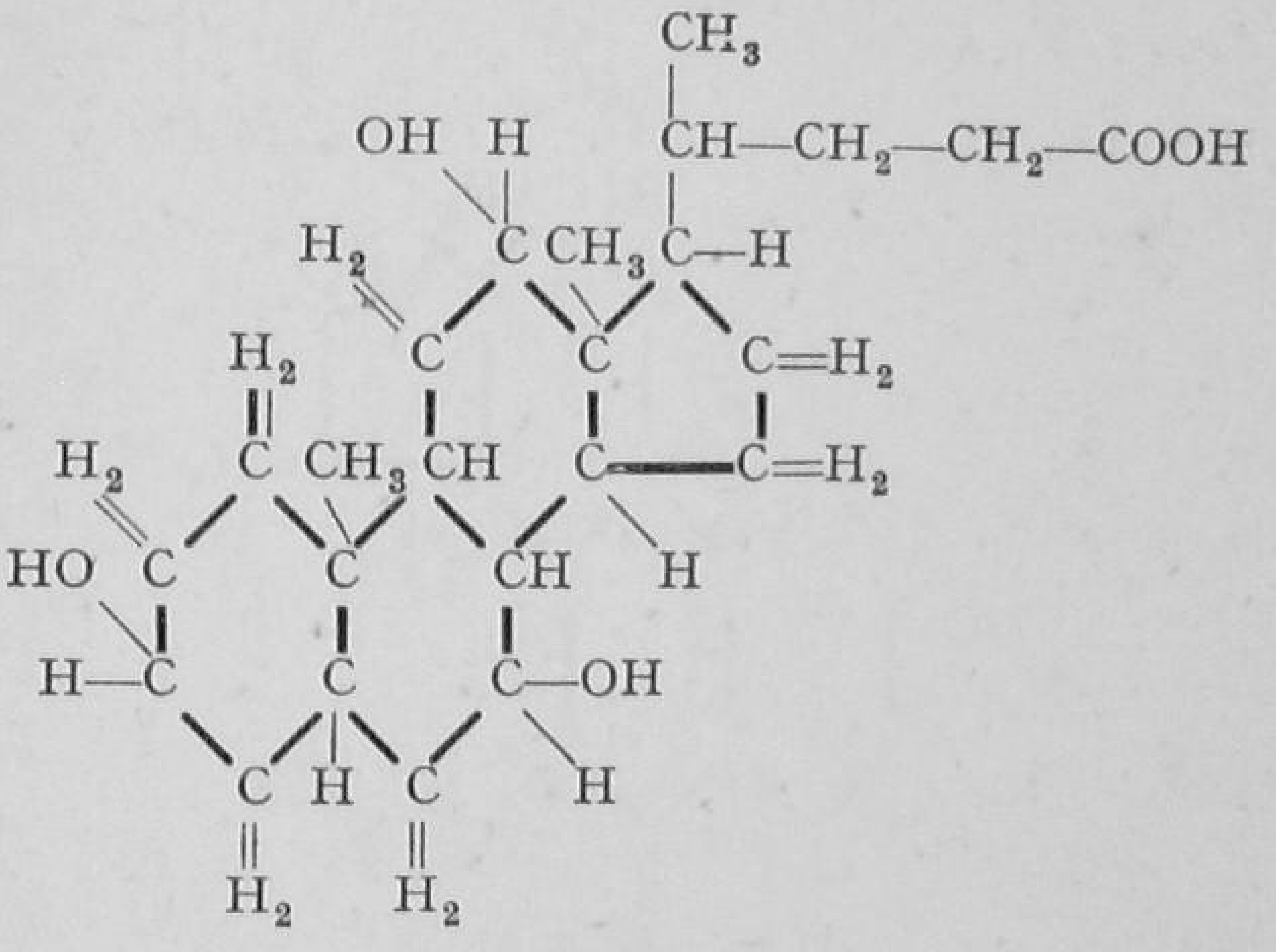


FIG. 72.—Cholic acid.

presumably, for much the same reason as the African native puts the vegetable poisons on his arrow-tips. Both groups of substances have as their basis a sterol skeleton just like cholic acid, but carrying somewhat different ornaments in the form of side-chains. In a vegetable heart poison a structure of this type is combined with a sugar molecule, whilst in a toad poison there is attached instead a nitrogen-containing side chain (suberyl arginine).

And finally we come to our last group of compounds related to the sterols and the sex hormones. It has been known for some time that the application to the skin over a long period of years of soot, coal-tar, and various products obtained from the latter, frequently results in the development of a carcinoma or tumour of the skin at the point where application has been

made. Workers in certain types of industry, such as sweeps, are particularly liable to such cancers, and, in the hope of shedding light on the problem of cancer as a whole, a very large amount of work has been carried out on mice treated by painting the skin with coal-tar. A very large proportion of such animals develop typical cancers.

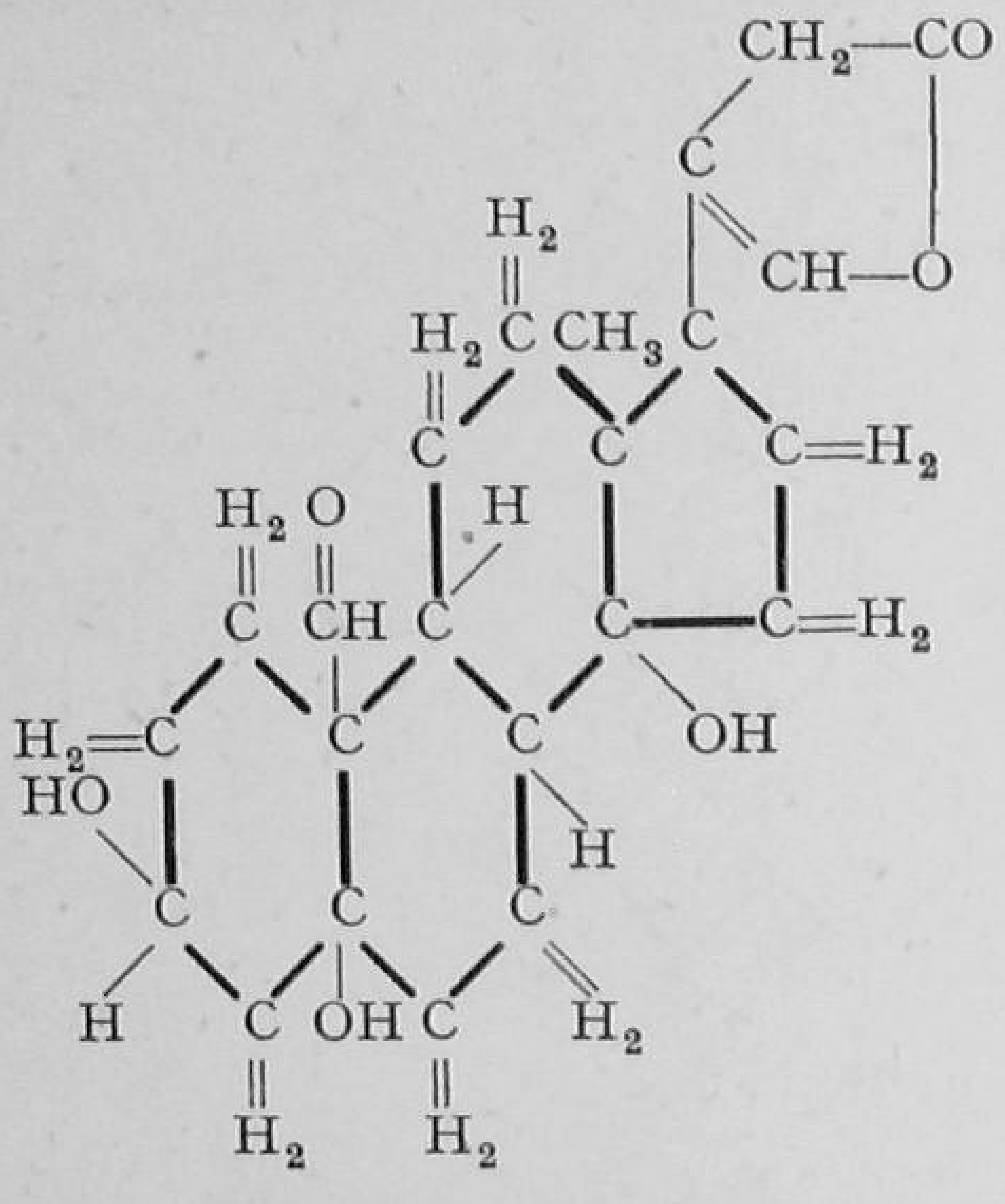
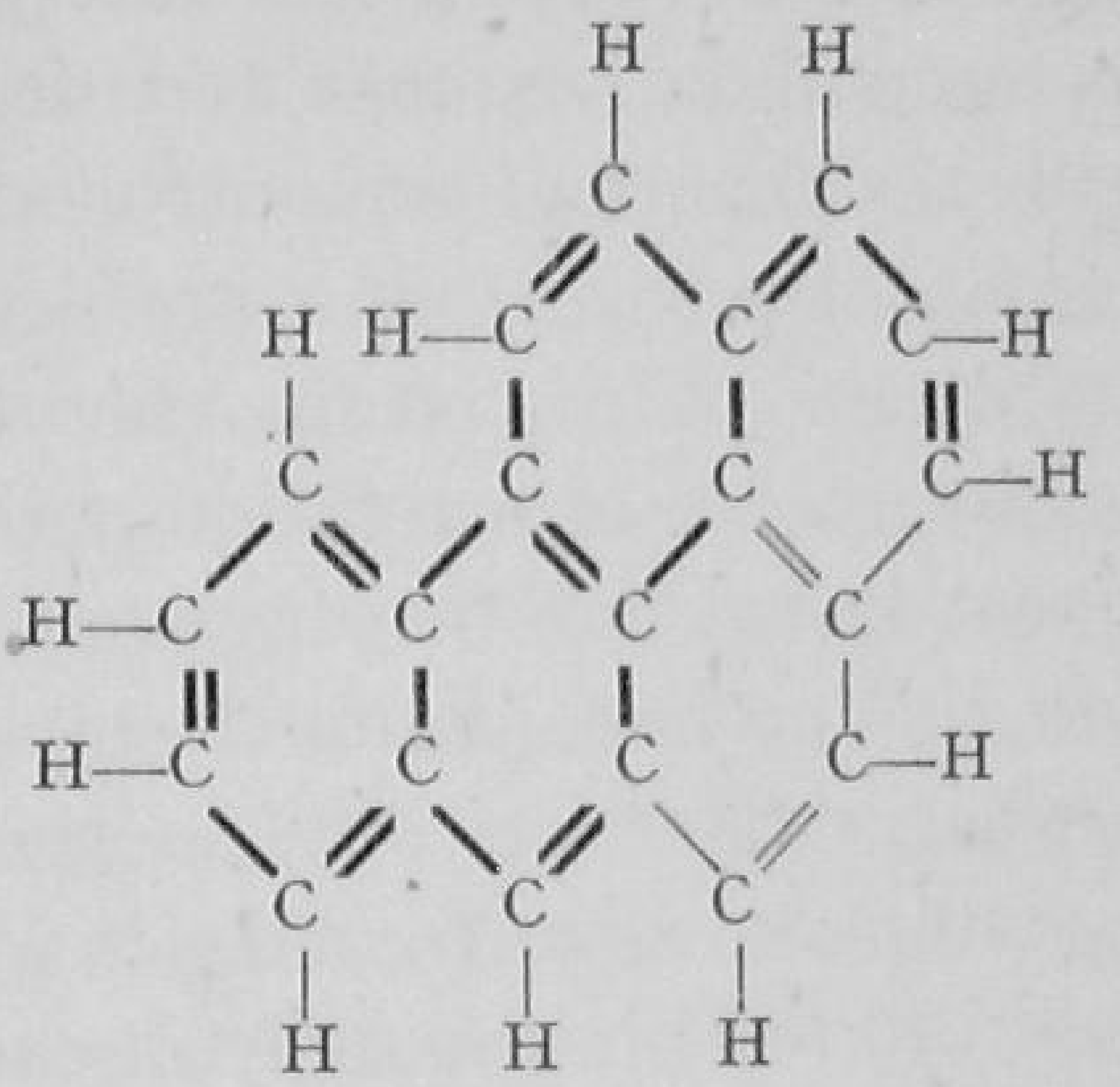


Fig. 73 (*a*).—Probable formula of Strophanthidin. This structure is typical of the heart poisons.

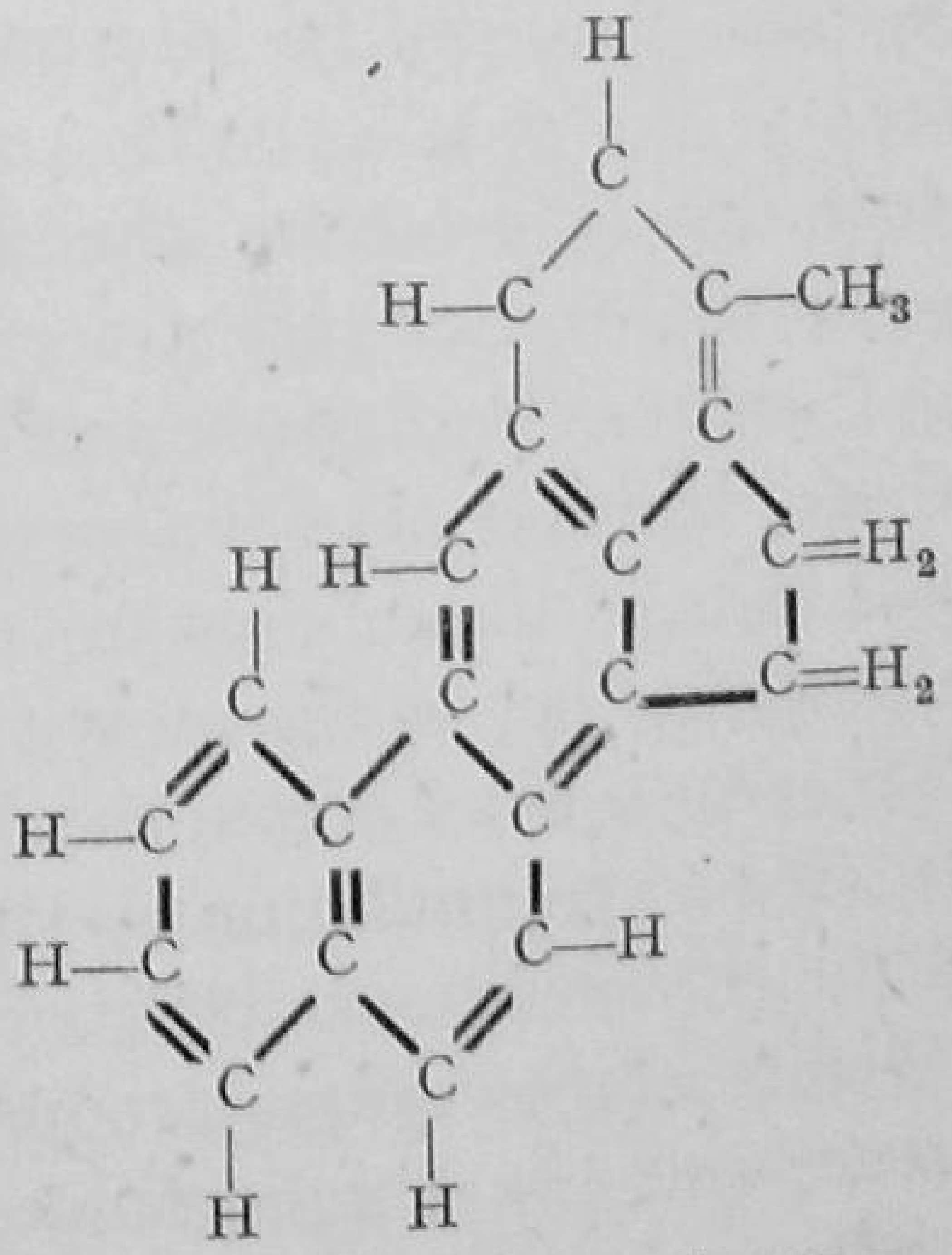
In 1932 Professor J. W. Cook announced the isolation from coal-tar of a pure crystalline compound which possessed the power of inciting the formation of skin cancers in a very marked degree. He not only isolated this compound; he found out its constitution, and confirmed the latter by synthesizing it in his laboratory. It is called benzpyrene and has the formula represented in Fig. 74 *a*. It contains five rings and it will be seen that four of them have a pattern very similar to, though not identical with, the ring pattern present in the sterols and sex hormones. The difference is that all the rings are six-membered, whereas in the sterols, one ring has five carbon atoms.

About the same time Cook found that quite a large number

of similar ring compounds are more or less effective in producing cancer when applied to the skin. Now one of the most active of all the cancer-producing compounds proves to be a



(*a*) Benzpyrene.



(*b*) Methyl cholanthrene.

FIG. 74.

substance called methyl-cholanthrene, Fig. 74 *b*. This may be produced in the laboratory from certain sterols by suitable chemical treatment, and as a glance at the formula will show, it contains the sterol ring system intact, although somewhat disguised in consequence of a fifth ring having been added.

Why is this work so important? It is because for the first time a perfectly definite cause has been discovered which will produce cancer, and as these compounds have known structures, a beginning has been made in the interpretation of the cancer problem in terms of the language and ideas of chemistry. Now cancer is really the abnormal, uncontrolled multiplication of a particular group of cells. It is a problem of abnormal growth and metabolism. Why certain chemical substances should cause this disturbance of regulation and co-ordination, we do not at present know, but the discovery of these compounds has made the problem a much more precise and limited one. In what mysterious way do these compounds react with living protoplasm so as to make it wild and uncontrollable? No doubt this will prove a difficult enough question; but it does suggest new lines of attack, lines which are all the more promising because they can be interpreted in terms of molecular structure.

Of course it does not follow from the discovery of the cancer-producing substances that all cancer is due to the presence of these. There may perhaps be more than one cause of cancer. There are, however, two important facts which workers in this field have not been slow to connect together. One is the clinical fact that one of the most common sites for the development of cancer is in an organ, the mammary gland, subject normally to frequent stimulation by the sex hormones. The second fact is the close relationship between the chemical structure of the highly active cancer-producing compound, methyl cholanthrene, and the sex hormones. The natural suggestion is that for some reason or another the sex hormones, or one of their precursors or by-products, is occasionally converted in the tissue by accident into one of the cancer-producing compounds. Of course, this line of thought is speculative, but some support for it may be found in the consideration that the action of oestrogenic substances is to encourage the growth and proliferation of those tissues on which they act, and such a proliferation has points of resemblance to tumour growth.

Indeed, several cancer-producing compounds have a definite oestrogenic action. The two effects are evidently related, so that a slight alteration of a compound which normally has the one action might easily convert it into one having the other.

These examples of chemical adaptation—the purines and pyrimidines the porphyrins, including chlorophyll, and haemoglobin, and the sterols and sex hormone group—are far from exhausting the whole field, but they are sufficient to illustrate the principle that the same structure can appear under various modifications serving many different uses. The question inevitably arises in our minds as to how this state of affairs has come about. Have haemoglobin and chlorophyll, for example, been independently discovered by animals and plants respectively? Or are they both derived from a common and probably simpler parent substance which came into existence in some very early type of life, perhaps some simple cytochrome required in the metabolism of primitive protoplasm?

It would be unwise to be dogmatic on such a question as this, but we can guess that independent invention of the same fundamental chemical pattern in different modifications is an unlikely contingency. If we examine a bat's wing, a horse's foreleg, a seal's flapper, and a human arm, and we realize that all these structures are fundamentally similar, we conclude that they are all derived from some prototype, modified in different ways so as to suit the various species and meet their particular needs. It is not difficult to believe that a somewhat analogous process of adaptation, this time of substances previously existing in the living cell, accounts for the appearance of the same chemical structure in so many different places and in so many different capacities. We are, of course, familiar enough with the idea in everyday life. When rubber was first discovered its uses were limited. With the invention of vulcanization it was found possible to employ it in an ever-widening range of applications—in the home, in industry, in medicine, and in sport. And, as new needs have developed, new methods have been found of treating the crude rubber

and of modifying the products, so that the material in its final state, whilst still fundamentally rubber, has various forms each adapted to some special needs. And so we have highly elastic rubber for bands and balloons, tough, hard-wearing rubber for soles and tyres, "aerated" rubber for pillows and sponges, rubber in the form of solutions for effecting repairs, as well as compositions containing rubber such as are used for insulating materials. As the need arises for a new type of material, research is undertaken with the object of providing it, and so as time goes on the old substance appears under new forms.

There is a continual interaction between a human community and the material resources at its disposal. The detailed development of the society is in some measure dependent on these material resources—a country without coal could never develop as England did in the nineteenth century—and at the same time the particular forms in which these resources are utilized depends on the conditions prevalent in that community.

Perhaps we may imagine the situation to have been somewhat similar in the case of the development of living organisms. We may picture the sex hormones, for example, not as a group of compounds created specially for the regulation of reproductive function, but as originally by-products in the metabolism of the natural sterols. The structure of the tissues of the organism, then, perhaps adapted itself so as to become sensitive to the presence of these compounds—the tissues found, so to speak, they could make use of them—and, by a gradual process of mutual modification and mutual adaptation, the whole complex mechanism of hormonal control has developed.

Similar considerations apply to the two other types of molecular pattern which we have discussed, and living organisms as we now know them would be quite unable to survive without these classes of compounds. They have become the faithful servants of living matter, humble but versatile, and for that reason indispensable.

CHAPTER XVII

STABLE AND UNSTABLE EQUILIBRIA

EVERYBODY at some time or another must have come across one of those funny little toy men that resist all attempts to knock them off their balance. He may look quite unstable, but give him a knock and, though he may have been flung almost horizontal, he at once springs up again as pleased as Punch at his obvious immunity to all the buffets of fortune. If we were to carve a similar figure out of wood, we should find that we could not balance it even on a smooth, level surface, let alone take liberties with it. This wooden model might perhaps be balanced on the nose of an expert juggler, but then only in order to evoke our admiration of his skill. To keep it upright, he has to be constantly on the alert, always moving slightly this way and that, ever correcting its perpetual tendency to fall away from the vertical "equilibrium" position. The wooden model, in fact, is unstable when balanced upright; the toy man, on the other hand, would never have been made but for his complete and imperturbable stability.

But, of course, the ideas of stability and instability are of importance not only in connexion with children's toys and feats of juggling. The question is of extreme significance in all sorts of practical affairs. A ship that cannot be relied upon to remain floating keel downwards is worse than useless. Indeed, everything to have permanence must be in some kind of stable equilibrium—an equilibrium which is unstable is for practical purposes not an equilibrium at all. The devices which may be adopted for ensuring this stability—the lead at the foot of the bobbing little man, the three legs of a stool, or the four wheels of a car—are interesting, but need not concern us here; it is sufficient if we realize that there are two types of equilibrium: in the stable type any disturbance

brings into play a force which opposes it; in the unstable there is no such automatic correction.

It is not only with regard to static equilibria that the ideas of stability and instability are of importance; a state of motion may also be stable or unstable. The case of an aeroplane affords a good illustration; when flying through the air at a constant speed and at a constant height, it is in a kind of steady state or "equilibrium". It is not, in this case, the position which is constant, but the motion. Now many modern aeroplanes will continue to fly safely ahead even though the pilot takes his hands and feet off the controls. If an accidental gust of wind tips the machine over, the construction is such that it rights itself automatically. Forces come into play which bring it back to its original position. In many of the earlier aeroplanes, on the other hand, the situation was very different. They were not self-correcting: if slightly tipped over, they would either continue to overbalance until they completely overturned or else they would enter upon a series of ever-increasing oscillations which would end in disaster. It was necessary, therefore, for the pilot to be constantly correcting the machine, neutralizing deliberately any small deviations from equilibrium. The steady state of motion was unstable and correction of disturbance was not automatic.

From the practical point of view, the question of the stability of a steady state of motion is often of great importance. The motor-car which at high speed develops a skid would not be nearly so dangerous if the skid quickly died out and the car returned automatically to its original course. But, as motorists know to their cost, when the car is moving fast skids must be deliberately corrected. The state of motion is in this respect unstable. A gramophone motor, controlled as it is by a governor, is a good example of a stable, steady motion. If by accident the motor is slightly slowed down, the mechanism so operates that the motor accelerates to its original rate.

The idea of steady motion may readily be extended so as to include all kinds of processes and activities, as well as simple

mechanical movement. Thus, for example, the whole of our economic system may be regarded as a process which in an ideal community would settle down into a kind of steady state. Small disturbances are bound to occur; for example, there may be a slight over-production leading to a fall in the level of prices. What actually happens is that this leads the producers to try to make up for their decreased profits by producing still larger amounts; but this floods the market to an ever-increasing extent and prices fall more and more. Where is this process to end? If there were no effective reaction it would be evidently only a question of time before the whole industrial system broke down. It would be ideal if the disturbance automatically brought into play a quick-acting restoring force which rapidly neutralized the original disturbance—just as the regulator of a thermostat switches on the heat whenever the thermometer drops. But an efficient economic thermostat is yet to be found, though the various experiments in "planned economy" so much talked of in recent years may point the way. What actually happens, as we know to our cost, is that although a reaction does set in, it comes late and is then too large: the speed of the economic machine does not merely return to normal but goes beyond, so we have the phenomena of alternate booms and depressions, with the threat of serious collapse always in the background.

The notion of stability is clearly of very wide application. No system is likely to remain for long in existence unless it is a stable one. In other words, it must respond to the disturbances, to which it is sure to be subjected, by reactions which bring it back to its original state—or at least prevent it deviating very far from it. These reactions may be purely automatic, in the sense that they are the necessary consequence of the structure of the system, as in the case of the bobbing man, or they may be generated by some special mechanism not really an essential part of the main structure, like the governor on an engine or the central organization of the "planned economy" State.

Often the compensation is not quite complete, as in a thermostat, the temperature of which usually falls a little when the outside air is very cold. But these various types of regulating and stabilizing mechanisms, though infinitely varied in structure and mode of operation, all serve the same general purpose. They secure the continued existence of the object or state or process which they control. Indeed, anything which has lasted a long time, especially anything of a delicate and complicated construction, is presumably so constituted that its stability is ensured. It must either be inherently stable, like a stone lying flat on the ground, or it must be fitted with some sort of stabilizing mechanism.

These considerations apply with especial force to living things. The various forms of animals and plants which exist in nature at the present day are just those which have managed to survive. Here the problem has a double aspect. We may consider either the individual animals and plants—which to ensure survival must be able to react to injury or disease or other disturbances so quickly as to neutralize their effects before any lasting damage has been done—or the species, which to ensure racial survival must also be stable. The individual at the best has a relatively short life; it is only for the race or species that even a relative immortality is possible.

Let us first of all, then, consider the problem of stability in relation to species. We know from the geological record that there are some species—or at least genera—which have survived almost unchanged for hundreds of millions of years. Others are of much more recent origin. Again, we know that many species which once flourished have now become extinct. Each species is constantly interacting with its environment—the latter in large measure consisting of the other species of animals and plants with which it finds itself in association. If over a long period the external conditions, such as the climate, remain constant, then we should expect that all these various species in course of time would settle down into a condition of stable equilibrium. Any inherently unstable

species would be weeded out. Small fluctuations might no doubt continue to occur, but no permanent change.

Of course, the equilibria which thus establish themselves in the biological world are rarely if ever absolutely steady states. Constantly minor fluctuations are going on: each species fluctuates in its numbers from season to season and even from year to year, whilst occasionally there is something approaching a large-scale periodicity, as in the famous case of the Norwegian lemmings, which every fourth year or so seem to suffer an acute crisis of over-population, solved only by the self-immolation of large numbers of these animals by marching *en masse* into the sea. Taken over a long period, however, the minor variations may be neglected, and apart from disturbances introduced by some novel and peculiar agency, such as the activity of man, the normal course is for nature to settle down into an equilibrium condition.

Every species is dependent on many others. Animals are dependent on plants and other animals for their food, plants are dependent on animals often for cross-fertilization or perhaps for keeping in abeyance some inimical parasite. So the equilibrium as a whole is a very complex one and in its details there is infinite variety. Infectious and parasitic diseases may be regarded as particular cases of this interplay of species, the disease organism and its victim ultimately settling down into a state of equilibrium with each other. In an animal community, for example, it will usually be found that certain infectious diseases are always present. Thus, rabies is endemic, that is to say, always present, among the canine and human populations of India; an alarmingly large proportion of our own domestic cattle suffer from tuberculosis; whilst everyone knows the dangers associated with the drinking of goat's milk in those countries where that animal is liable to suffer from Malta fever. In all these cases the disease goes on from year to year, fluctuating perhaps in intensity, but showing no violent deviations. A steady state of disease has been established which in the absence of external

changes, such as an anti-tuberculosis campaign by man, will be a permanent feature of the community.

In practice we often find severe epidemics superimposed on a relatively steady endemic state. Thus plague is endemic in many parts of the East, yet there have occurred from time to time epidemic outbreaks, often of disastrous severity. No distinct line can be drawn between these major outbreaks and the minor fluctuations which almost inevitably disturb the even flow of any uniform process of disease; the difference is a quantitative one, and the factors involved are numerous and difficult to evaluate. But with the development of experimental epidemiology on the one hand—a good beginning has already been made by Greenwood, Topley, and their collaborators with their work on mice epidemics at the London School of Hygiene and Tropical Medicine—and the development of a mathematical theory of the incidence of disease in communities on the other, a deeper insight into these problems of human and animal diseases may in due course be expected.

But there is one exception to the general principle that any state which has lasted for a long time is necessarily a stable one. True, the exception, though common enough in practice, is of rather a curious type; some might question whether it is really an exception at all. Let us, for example, imagine an isolated oceanic island inhabited by a race susceptible to, let us say, smallpox, but actually quite free from the disease. The population on the island will have settled down to an equilibrium state which will be perfectly stable as long as the island remains isolated. But let us suppose that a few cases of smallpox accidentally reach the island. Then one of two things may happen. Either the population may be so scattered that the chance of infection of healthy persons may be smaller than the chances of death or recovery of those who are ill, so that the disease may die out in a relatively short time; or the chance of contagion may be so great that the disease spreads and a substantial proportion of the whole population becomes infected with the disease, which then remains endemic in the

community. In the first case the disease-free state was really a stable one; in the second, it was essentially unstable, but nevertheless persisted as long as the virus was rigorously excluded.

The case just considered is an artificially simple one, but it does represent a situation which undoubtedly occurs in practice in more complicated forms. Our knowledge of diseases is most complete in the case of those which affect human beings. A considerable amount is also known of the common diseases of domestic animals, but much less about those which affect other species. Now the conditions of life of man and his domestic animals are highly artificial and complex, and so there are usually many factors of varying degrees of importance which determine the prevalence and deadliness of a disease. However, in spite of these complications it is not difficult to point to examples which illustrate the existence of unstable states of the kind that we have just described. There are cases on record of native tribes, for example, among the Indians of Canada, where tuberculosis was entirely unknown until it was introduced by the white man. Immediately, the disease spread rapidly, and soon the tribes were decimated. The original unstable equilibrium was disturbed and so disaster ensued.

Again, we all know how great are the precautions which must be taken if foot-and-mouth disease is not to be allowed to obtain a foothold in Britain. Once established, this disease would sweep throughout the country like wild-fire, causing enormous losses to the farming community. Evidently with respect to foot-and-mouth disease virus, our population of sheep, cattle, and pigs is in a condition that would be highly unstable were it not that the Ministry of Agriculture acts in this connexion somewhat like the governor of an engine, inducing reactions which stamp out any threatened epidemic and restore the original disease-free state. In the old days an outbreak of plague or smallpox tended to spread throughout the community. At the present time, thanks to our changed

habits of life, to vaccination, and to the various measures which have been introduced for the improvement of public health, these diseases are no longer the same deadly threat; if by any chance one or two cases occur, the probability of the disease spreading is so small that the outbreak quickly comes to an end.

The question may be asked why persistent unstable states are ever found in nature at all. In cases such as that of the American Indians, the answer is clearly that the germ of the disease had never previously been introduced. But it is only by some strange chance that any community, however isolated, could have escaped exposure to infection for an indefinite length of time. In some cases of persistent unstable states it is likely that the condition now unstable was once a stable one. In any community various factors tend always to be changing; a change in habits as regards diet and housing may exercise a decisive effect on the infectivity of some disease by altering either the general resistance of the hosts or the closeness of contact between the infected and the uninfected. Often these changes take place gradually and pass almost unnoticed. The result may be that a community originally in stable equilibrium suddenly wakes up to find itself in a quite unstable condition, liable to be devastated by an epidemic of, say, influenza or tuberculosis, should the infection be accidentally introduced.

But it is not only with respect to disease that instability may develop in a community. The whole process of civilized life is really a delicately balanced equilibrium. We have already seen how a civilized society may be economically unstable. Even more important is the question of the stability of the life of the community as a whole. In considering this wide question it is not possible to keep separate the biological and economic aspects. The standard of life of the society, its social and economic structure, affect the fundamental biological processes.

The health of the community, the death rate and the birth

rate, are intimately connected with social and economic conditions. We all know how both deaths and births tend to become rarer in the Western world as the standard of life goes up. The fall in the death rate is natural; one would expect, however, that in a less sophisticated society wealth and abundance would be followed by high fertility. In an ordinary animal community rapid multiplication is the usual response to an abundant food supply. It is evident, however, that in the case of man under the present social order with which we are familiar the usual reaction does not occur. Even in countries such as Japan, so different in many ways from the countries of North-western Europe, one of the results of the process of "Westernization" has been a definite fall of the birth rate. The deep-seated nature of the forces which are producing these results is shown by the fact that they seem to defy all attempts to neutralize them. Even in Fascist Italy the birth rate continued to fall, in spite of the combined efforts of Signor Mussolini and the Roman Catholic Church.

Whatever may be the real explanation of this paradoxical relation between the standard of life and the birth rate, it is undeniable that it is an effect of great import. If the birth rate falls below the death rate—and it already seems inevitable that it will soon do so in the countries of North-western Europe—then the continued existence of the community is threatened. It almost looks as if the individualistic stratified society, which in the eighteenth and nineteenth centuries appeared so natural and so stable, contained within it the seeds of its own decay, as if it were essentially an unstable form of organization.

However, it is not only in respect of numbers that the community may become unstable; the population may also alter in quality, and a collapse in this respect is equally likely to prove disastrous. If, other things being equal, the fertility of small men were greater than that of tall men, then we know the average height of the population would decrease. Now there is every reason to believe that what is true of a physical

quality such as height also holds of mental and moral qualities. Thus, if those who possess intelligence or prudence or courage are less fertile, other things being equal, than their neighbours who lack these qualities, then these will gradually become rarer and rarer.

Now in the more primitive communities the conditions are usually such that the virtues essential for that form of society ensure the reproduction of those who possess them. In a warrior tribe, for instance, the most courageous get the largest number of wives and so are likely to have most children. But in modern civilization the important civic virtues, respect for law, prudence, foresight, are in no way likely to lead to large families on the part of their possessors. Indeed, under modern conditions it would seem that, other things being equal, it is the careless and improvident who are likely to be most prolific. If this is so, we may expect the character of the population gradually to alter, and in such a sense as to become less prudent and less self-restrained.

This might be a good thing; it is dangerous to be dogmatic on such matters. It is more likely, however, that such a change would threaten the whole fabric of the highly complex and artificial communities in which we now live. Industry, government, public health—all these are maintained only by careful foresight and scrupulous attention to detail. Once these essential moral qualities in the population are lacking, the whole social structure may disintegrate. Is this form of instability not perhaps our greatest threat to-day?

The idea that particular forms of social organization may be but transitory stages in human evolution is no new one. The panorama of history, with its succession of civilizations, Egypt and Babylon, Greece and Rome, each rising to power and glory only to fade away in disintegration and decay—forcibly emphasizes the instability of the more complex types of human civilization. We may contrast with them the permanence of the organized societies of more primitive organisms, such as bees or ants. Generation after generation these

communities go on without change; the individuals are different yet the organization remains the same. But this stability is achieved only at a cost—these insect communities are necessarily inflexible in their form, frozen and inadaptable. The restless energy of the human race, with its infinite variety and almost boundless possibilities of progress, is perhaps preferable, after all, to the stable stagnation of the ant-hill.

It is not only in connexion with species and communities that the problem of stability is met with; it is also of the greatest importance in relation to the individual organism. The animal or plant is constantly subjected to disturbing factors, which are ever buffeting it about more or less violently. If the disturbance threatens to result in the paralysis of some of its essential functions, then its very existence is at stake. To such disturbances, then, it must react by prompt and efficient means. Let us consider a few examples which illustrate this general principle.

We have all suffered from a common cold. We know how the attack is frequently heralded by sneezing and shivering; how this is followed by running at the nose and eyes with perhaps a headache and a high temperature; how these symptoms gradually disappear, to be followed by a stage during which we discharge a thick, unpleasant mucus from our nose or cough it up from our air passages. But in a few days this likewise passes away, and so we return again to our normal state, none the worse for our chill. The body has reacted vigorously and successfully to the infection. We were unpleasantly conscious of the disturbed conditions while they lasted, but we had early mobilized our forces to oppose the invading germs and soon had routed them completely. Evidently in respect of such a disturbance our equilibrium was a stable one.

But it does not always happen so. Sometimes the results of the battle are indecisive, or the invaders may even win. Infection may spread down our windpipe and into our lungs. Pneumonia develops. Our body then mobilizes its forces for

a much more serious and critical struggle. Perhaps it may manage to save the situation, but it may fail. The invaders are then supreme, and the forces at the disposal of the body crumple up.

The disease of diabetes affords another good illustration of how an overstrained regulatory mechanism may break down, and incidentally how medical science may step in and help to re-establish the equilibrium. Diabetes is due in most cases to a failure of the organ known as the pancreas (Fig. 52) to produce sufficient insulin, a substance which encourages the tissues to use and store sugar, and is produced by the pancreas in extra quantity whenever there is an excess of sugar in the blood, as for example after a heavy meal. In a healthy individual the pancreas acts as a regulating mechanism, adjusting the consumption of sugar to the supply. Without insulin, the tissues are unable to make use of sugar, one of their chief sources of energy, and so the whole economy of the body is seriously disturbed. The accumulation of sugar in the blood and its excretion in the urine naturally follow. With all this sugar waiting to be consumed, the already enfeebled pancreas does its best. Indeed, it works itself literally to death. It can take no rest; it becomes more and more fatigued and its power to produce insulin dwindles away. The symptoms of the disease become increasingly more serious, and in the absence of treatment collapse and death is the almost inevitable result.

In a disease such as this the obvious thing to do is to discover some method of breaking the vicious circle. Sugar, the normal food of the tissues, is here worse than useless; it is almost a poison, hastening the deterioration of the pancreas which was the original cause of the disease. Evidently, then, the excess of sugar in the blood and organs must at all costs be reduced. Foods which contain sugar or which readily give rise to it might be rigidly excluded from the diet. The energy requirements would then have to be satisfied as far as possible at the expense of fats. But though fat can be burned to

supply energy there seems to be a strict limit to the extent to which we can do this. Although in the old days the best that could be done was to reduce the carbohydrate intake and increase the proportion of fat, the result was an uncomfortable compromise, only to be tolerated because nothing better was available.

But in diabetes, as in a number of other diseases, our close family kinship with the lower animals has been our salvation. Being not very distant cousins of the cow and sheep we are constructed on very similar lines. Our physiology, like our anatomy, is really very analogous to that of the lower animals. The insulin in the pancreas of a domestic animal killed in the slaughter-house is indistinguishable from the insulin produced in our own bodies. Obviously, then, all that is required in order to treat and control human diabetes is to extract the insulin from the sweetbreads of dead cows and sheep and pigs, and get it in a form suitable for administration to human beings.

Of course this was not, in practice, nearly as simple as it looks on paper. It required many years of elaborate research work on the aetiology of diabetes, and then the final isolation of insulin in a usable form by Banting, Macleod, and their colleagues in Toronto, before treatment with animal insulin became a practical method. When administered to the patient, usually by injection under the skin, it enables the tissues of the body to deal with sugar in the normal way. The exhausted pancreas is given a respite and the process of deterioration held up. Indeed, it may even begin to recover and gradually regain a substantial portion of its normal activity. Consequently it is often possible gradually to reduce the dose of insulin, and sometimes ultimately even to dispense with it altogether. The vicious circle has been broken and equilibrium has been restored.

The disturbances to which the cells of the body are subjected in the course of a disease such as pneumonia or diabetes are of a gross and obvious kind. Death occurs only as the climax

of a series of quite drastic changes. In respect of certain environmental factors, however, the living cell is much more fastidious, and even minute changes of these may result in a grave derangement of function. We have already seen in another connexion how important it is that the fluid in which a tissue is bathed should retain its proper concentration of salt. Now, as important as the salt content of the tissue fluid is the balance of acidity and alkalinity; the tissues must be neither too acid nor too alkaline in reaction, but just at the correct point. In the case of the blood, this correct condition is one of very slight alkalinity. A quite small departure of the reaction from this point is very serious, and for this reason the blood and other body fluids are equipped with stabilizing devices.

Recall once more our little toy man, who, when he was pushed from the vertical, returned to his original position. We may give the reaction of the blood a push by adding to it a few drops of acid. In the case of pure water this would result in the development of a markedly acid reaction—pure water is in a very unstable equilibrium as regards its reaction; but unless the acid is very strong indeed the blood will be hardly affected. Unlike pure water, it replies to the push; it resembles the toy which bobs back to its original state, or very nearly to it. In respect of reaction, the equilibrium of the blood is a very stable one.

This property of most biological fluids and tissues and certain artificial solutions to resist attempts to alter their acidity or alkalinity is of very great importance; we speak of such a fluid as being highly "buffered". The use of this term suggests that the action of such a solution is somewhat similar to that of the buffers at a railway terminus, and indeed the analogy is quite a fair one. The cushion-like effect of the springs takes up the violence of the impact; but in the solution there are no mechanical springs, instead it contains certain dissolved substances which bring about the effect. For example, if we take a solution containing both sodium acetate

and acetic acid, the addition to it of a little hydrochloric acid will convert some of the sodium acetate into acetic acid, a small quantity of sodium chloride being also formed. The latter has no effect on the reaction, and the acetic acid, being a very much weaker acid than the hydrochloric acid which was added, produces only a very slight disturbance. Thus the acidifying power of the hydrochloric acid is very much less when it is added to such a solution than when added to pure water. In a similar way, the effect of the addition of sodium hydroxide is also reduced; in this case, a little acetic acid is converted into sodium acetate.

In the blood the system is considerably more complicated. Sodium bicarbonate plays roughly the same part as the acetate in the above example, and it is even more effective as a buffer, because the weak carbonic acid produced can be eliminated as the gas carbon dioxide and so still further lessen the effect of the added acid. But the prettiest trick is still to come. The haemoglobin in the blood, as every schoolboy knows, combines with oxygen. As the blood passes through the lungs it forms oxyhaemoglobin, which gives up its oxygen when the blood again reaches the tissues. Now both these compounds are weak acids, but haemoglobin is much the weaker of the two and its salts are therefore more alkaline. When oxyhaemoglobin gives up its oxygen to the tissues, therefore, the blood tends on this account to become more alkaline—*at the very point where the carbon dioxide coming in is tending to make the blood acid*. Conversely, in the lungs, the haemoglobin by combining with oxygen, tends to make the blood less alkaline and so compensates for the loss of carbon dioxide. Thus, in producing haemoglobin nature has contrived to kill two birds with one stone; for this compound is not only specially adapted for the carriage of oxygen, it also facilitates the easy transfer of carbon dioxide in the opposite direction. By such means an exceedingly stable equilibrium is maintained in spite of the severely disturbing factors to which the reaction of the blood is subjected. In the absence of buffering,

the large quantity of carbon dioxide which the blood must carry from our tissues to our lungs would itself be sufficient to alter the reaction to one of definite acidity, whilst the lactic acid produced during exercise would completely upset most of the activities of living tissue.

The course of evolution has in general been marked by increased complexity in the structure and function of the individual, and at the same time increased stability in respect of outside disturbances. The more complicated and ingenious the machine, the more easily is it damaged by being knocked about and the more necessary it is to protect it from all deleterious influences. Now in connexion with any physico-chemical system, one of the most important factors is temperature. It is not surprising that it is the highest types of animals, the birds, the marsupials, and the mammals, that have developed the power of regulating their own body temperatures. The cold-blooded animals are in this respect at the mercy of their environment. Their temperature varies with that of their surroundings, being but slightly higher in consequence of their relatively low rate of heat production. In the warm-blooded animals the body temperature remains almost constant—so much so, indeed, that a rise above normal of only a couple of degrees is sufficient to alarm the doctor. This extremely stable poise of body temperature obviously implies a very delicate regulating mechanism. The disturbances which might be expected to affect the body temperature are often of very great magnitude. A man may find himself in Khartoum at a temperature of over 100° F. or in a Siberian winter with over sixty degrees of frost. It is clear that even with the advantages offered by the power of varying the amount of clothing—and other animals, it must be remembered, do not possess even this—the preservation of an almost uniform temperature implies a control or governor-mechanism of a very efficient type. Some of the devices which form part of this mechanism are familiar to us all.

In very hot weather or after violent exercise we sweat in

order to get rid of heat in the form of the "latent" heat required to evaporate water—sweat which drops or is wiped off is wasted effort. In very cold weather, on the other hand, we shiver—nature's object here is to produce extra heat by the activity of the muscles. The details of these temperature-regulating processes are still in some respects obscure. There is a centre in the brain, the heat centre, which acts as a kind of master control and co-ordinates the various special devices. The body may be likened to an accurate thermostat and the heat centre to the thermostatfc device which controls the works.

These are but one or two examples which bring out the importance of stability, both of form and of function, for the living organism. For the individual, as for the community or species, instability means death. But all living things must die; the individual cells of our bodies develop and function, but sooner or later become inefficient and senile, and are ultimately replaced by younger and more vigorous ones. Their stability is only relative; the adverse influences ultimately triumph and the cells disintegrate into the dust—and gas—out of which they are made. And so it is, too, with individual animals and plants. Like the cells of which they are composed, they grow up, play their little part on the stage of life, and then inevitably die. All their efforts to stabilize themselves as mechanical systems have met with only partial success. Immortality is still the prerogative only of the Gods. Or should we regard the species as immortal? Certain it is that some species have continued through long periods of geological time with but little change. Shells of *Lingula* are found in rocks laid down over five hundred million years ago and they are indistinguishable from shells still found abundantly round our coasts. In the case of bacteria and unicellular organisms in general the survival of the species implies the virtual continued existence of individuals and perhaps in the same sense we must regard the germ cells of the higher animals and plants, the ova and spermatozoa, as immortal—at least as far

as the species is immortal. In all these cases, it is clear, the struggle for stability has met with striking success.

Of course there are no grounds for assuming that any species, however stable it may seem to be, will go on for ever. Many have already died out; whole families and even orders of animals and plants which at one time flourished abundantly have become extinct and are known only by a fossil skeleton or the carbonized impression of a leaf or a stem. Indeed, of all the numerous species which have come into existence, by far the larger number have already succumbed to the forces of disintegration, from without or within. Whether all species will ultimately meet with the same fate, whether life itself will ultimately vanish from the earth—it would be rash to be dogmatic on such questions. It is true we must contemplate a world which in the very distant future is likely to become ever colder and colder, until with the gradual decay of the sun as a source of light and heat the continents and the oceans and even the air itself have frozen into the semblance of perpetual death. But as life develops and becomes more complex it can become more and more independent of the environment. In man, we see this independence at the highest point so far realized. Civilization and human progress may indeed be regarded as the conquest by man of his environment and the attainment of control over his own destiny. The extreme adaptability of man, coupled with his deliberate control over his circumstances, give him unprecedented advantages in the struggle for survival. Can anyone, then, predict with certainty what man's ultimate fate will be—whether the species will collapse from internal decay or be overwhelmed by the force of irresistible circumstances from without, or whether it may not adapt itself and its environment to meet new conditions as they arise, and so perhaps achieve immortality?

CHAPTER XVIII

NO-MAN'S-LAND

IN the days of the scholastic philosophers much time is said to have been spent and much mental energy used up in trying to answer the question, What is the smallest possible number of grains which would make a heap? Everyone would agree that a thousand grains would do so and that two grains would certainly not. The number was therefore greater than two and less than a thousand, what then is it? Of course, it is quite obvious that a definite answer is not possible, for the very notion of a heap involves a certain lack of precision in regard to the numerical definition of its lower limit. The question, in fact, does not possess any definite answer and any attempt to arrive at a precise number can only lead to fruitless discussion and futile argument.

The question of the number of grains in a heap may seem to us a trivial one, but the point involved, the realization that every question, even though grammatically correct and logically significant, has not necessarily an answer, is really a very important one. We have already seen in Chapter III how important is the bearing of this observation on the modern developments of physics. Until quite recently no one doubted but that it was entirely permissible to inquire what was the position and what was the velocity of any particle. They assumed that these data existed even though not actually known, and so Newtonian dynamics started off by assuming that every particle possessed both position and velocity. We know now that this is all wrong; but the path to the realization of the true state of affairs has been a long and difficult one, and it took almost a generation of very perplexed physicists to see that they had been making the mistake of the old philosophers: they had

assumed that a simple question necessarily possessed a simple answer.

But how are we to know whether any particular question is answerable or not? It is not easy to give a concise general reply to this inquiry: one reason for the difficulty is that the "unanswerableness" of a question may not always be due to the same cause. The question may have no real meaning because the definitions of the words employed in putting it are not consistent with the question having any answer. Thus the definition of a heap is "A pile or mass heaved or thrown together", and there is clearly no smallest number which can be so thrown together.

It should be noticed that, as in many similar cases, a slight difference in the wording of the sentence may result in an entirely satisfactory question. If we ask, for example, for a number such that any heap must contain a greater number of grains, a perfectly good answer can be given; the number 2 would meet the case.

As to the position and velocity of a particle, there does not seem to be any logical reason why the question should have no definite answer. In the case of particles of ordinary size, position and velocity seem to be capable of very exact measurement, at least relatively to other material bodies. The difficulty arises when we extrapolate: when we assume that what has meaning in relation to millions of elementary particles continues to have meaning for a single one; that what holds in one region of our scale of magnitudes (Chapter I) holds equally well for every other region. It is clearly a fallacy to assume that because we call our fundamental entities "particles" they possess the attributes of ordinary particles, such as sand grains or lead shot. The lesson of Modern Physics would seem to be clear, that we can only be certain that any object has some particular character when that character has actually been observed. In other words, the proof of the pudding is in the eating. If, on ther other hand, the attempt to answer some question, or even the assumption that some

question has a definite answer, leads to inconsistencies, then it is time to suspect that the question is really meaningless. Perhaps the error involved is only a slight one, perhaps only a minor change in the form of the question is required. Possibly we may have been searching for a precise answer where only a slightly vague or blurred one is feasible: exact answers, as we have seen, rarely or never exist.

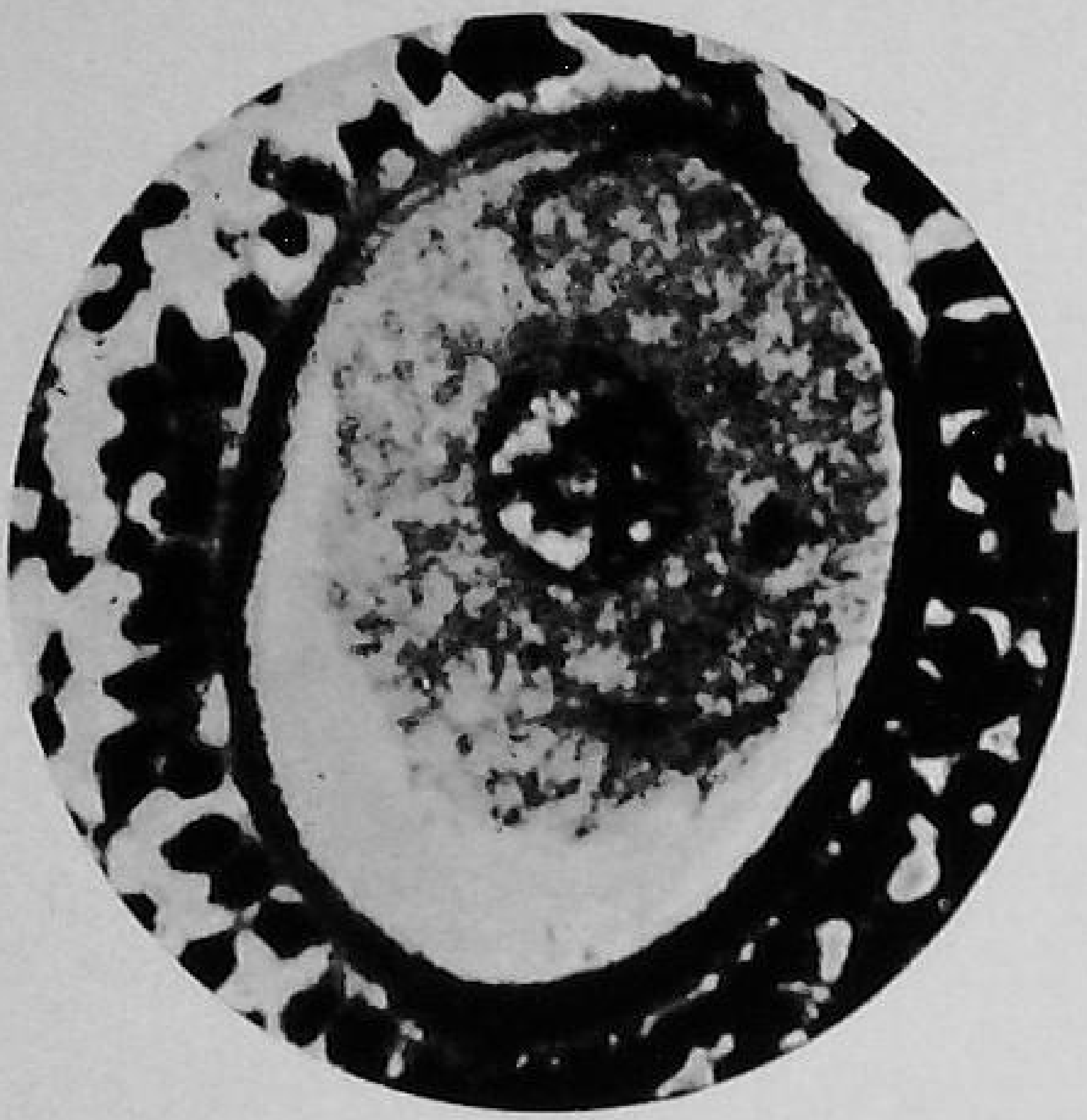
If these subtle traps, these questions without meaning and problems without solutions, are met with in the relatively simple sphere of the inanimate world, how much more must we be on our guard against similar snares when we are thinking about the deeper problems of life and consciousness, and the relation of the living to the dead. It is easy to ask questions such as, "When did life begin?" or, "At what instant does death take place?" to which for all we know it may be really quite impossible to give a precise answer. One cannot, for instance, say that death takes place when breathing ceases—many people have recovered from drowning, after a few minutes' immersion, when they have not only stopped breathing but actually lost all power to resume it spontaneously. Without artificial respiration they would undoubtedly have been beyond recovery. Even the stoppage of the heart's beating does not necessarily imply death. Surgeons are sometimes able by suitable heart massage to make a heart begin again after it has stopped, as a motor-car engine which has stalled will pick up again after a touch of the starter or a twist of the handle. In cases where the heart has been stopped for considerable time—even minutes may have elapsed since the last beat—the injection into the heart of a small quantity of the drug adrenaline is sometimes sufficient to start it off again; and the patient or animal, who may be said to have been dead according to all usual criteria, may ultimately recover completely. It is of great interest to observe that in dogs, if the stoppage of the heart has been too prolonged, say fifteen or thirty minutes, even though recovery takes place there may be signs that certain important brain centres have been

permanently damaged during the period when the tissues were unable to obtain their usual supplies of oxygen. Evidently, though the animal as a whole is certainly not dead, the decay of death has already begun.

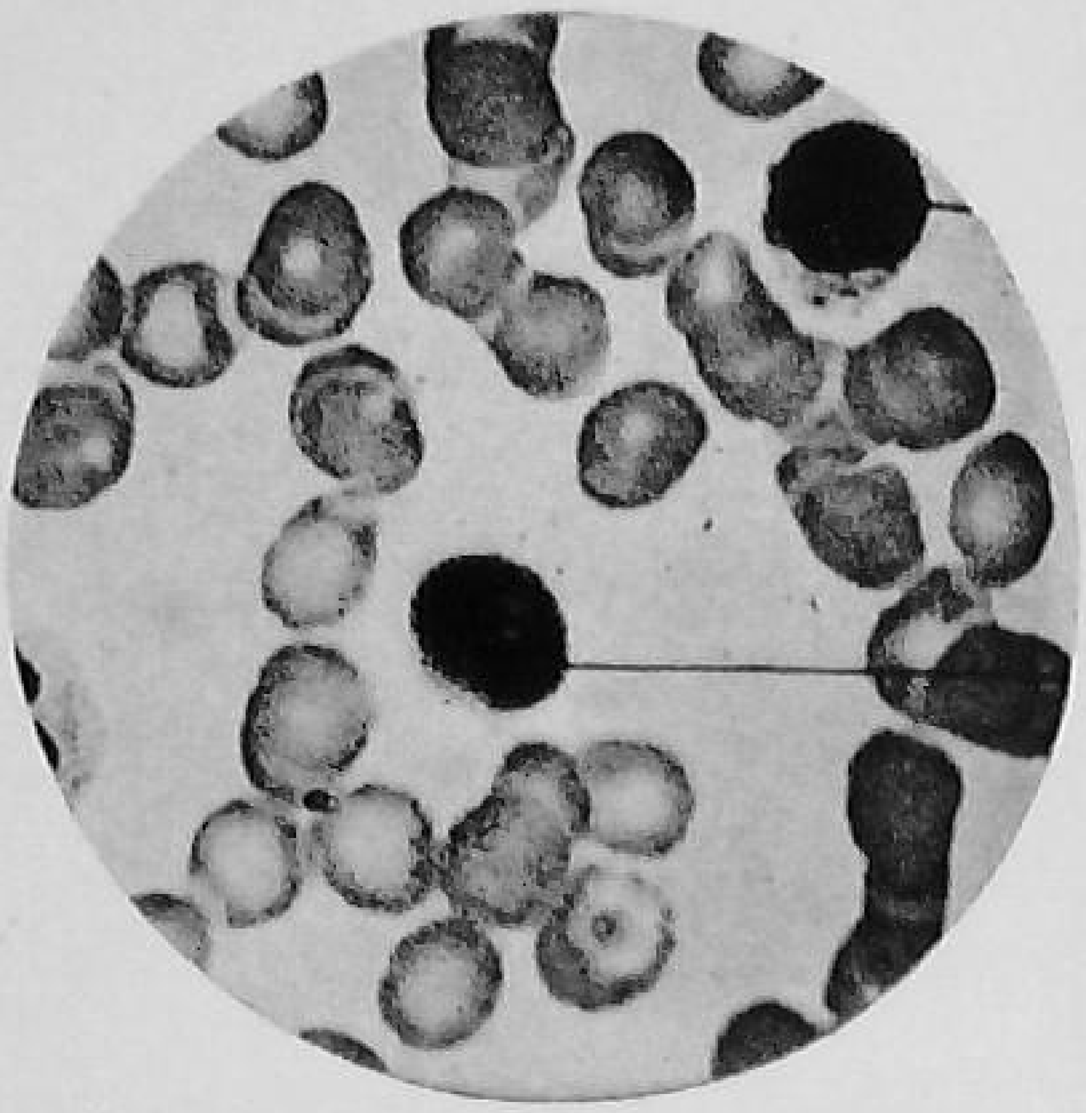
Whilst the delicate and important brain cells may give evidence of incipient disorganization even before the body as a whole is beyond all power of recovery, there are, on the ather hand, cells in the body which may go on living long after death in the ordinary sense has taken place. Indeed, it has been found possible to grow cells outside the body altogether, to cultivate them in a suitable medium inside a glass flask, just as one cultivates bacteria or other micro-organisms. Certain types of cells, especially those derived from embryonic tissues and in consequence particularly vigorous and adaptable, develop and multiply with relative ease, and may be cultivated for long periods of time. These cells may go on living long after the organism from which they were originally derived is dead.

These considerations lead us to the conclusion that the distinction between the living and the dead is not always as clear-cut as we are apt to suppose. Evidently the question, At what time exactly did Mr. Tompkins die? does not always have a precise answer. We may know that he was alive, say, at twelve noon; we may also know that he was quite definitely dead in the ordinary sense of the term, and beyond all hope of recovery, five minutes later; we may reduce the period of uncertainty to one minute or even to a few seconds by choosing a suitable form of death—but the more exact we try to be, the more difficult it is to be certain. The difficulties are only increased if we take into consideration the facts concerning the survival of individual cells or groups of cells after the death of the body as a whole. Death cannot, in general, be localized as occurring at any one particular instant—just as the smallest number of grains in a heap is not represented by any one definite number.

We have, then, in time a kind of no-man's-land separating

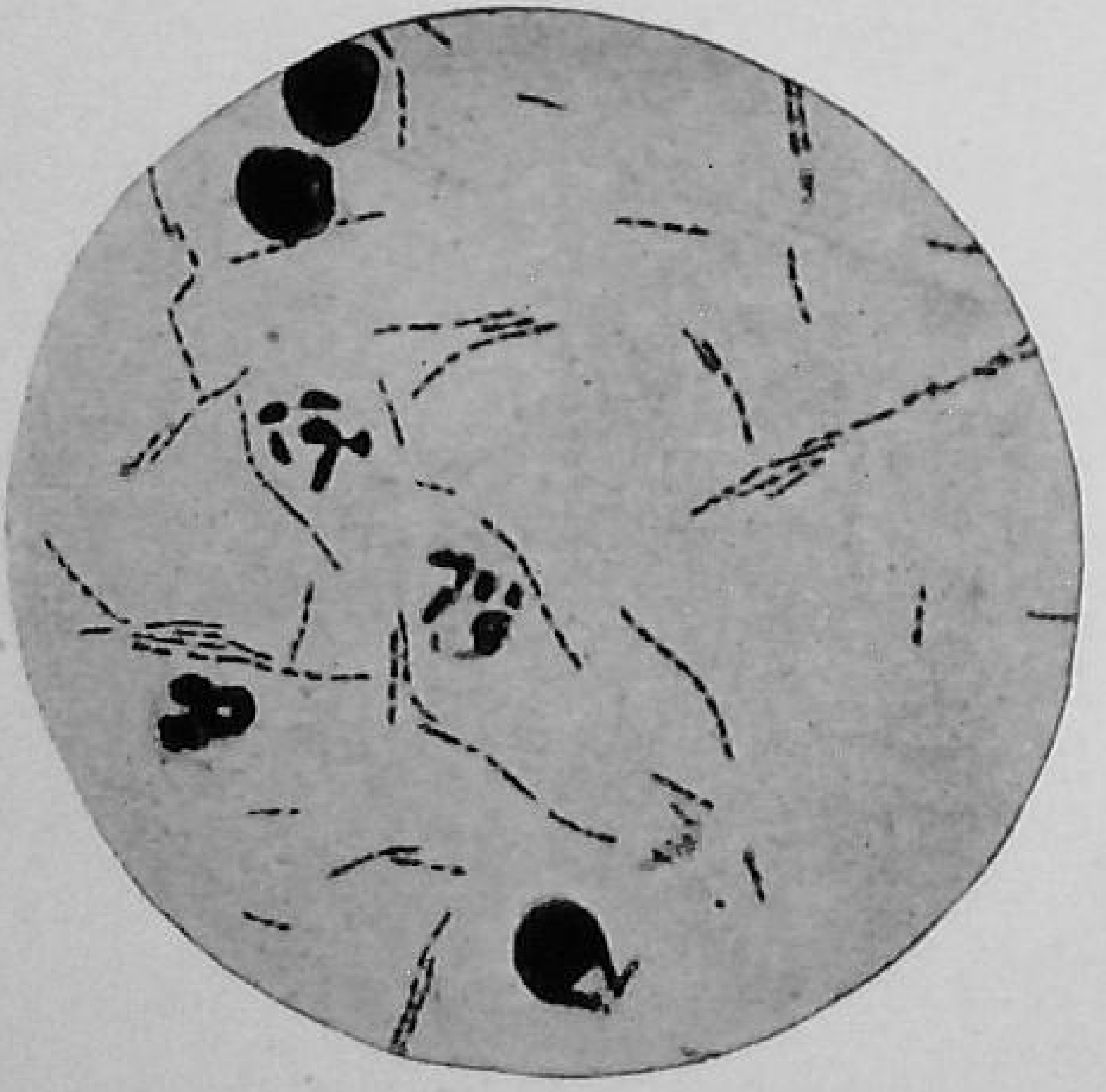


The Human Ovum.
× 500.



[*From photomicrograph by Lt. Col. W. F. Harvey.*

Human Red Blood Cells.
× 500.



Anthrax Bacillus.
× 750.

Tubercle Bacillus.
× 1,000.

Four types of cell, located at points 17, 14, 12 and 11 respectively, on the scale of magnitudes, page 10. Observe that the human ovum is a million times as large as a tubercle bacillus.

the living from the dead—a land which belongs to both and yet belongs properly to neither. It is natural to inquire next about another transition between living and dead. In this case the boundary is not in time, for it is the boundary between the things which are living and the inanimate objects—sand, water, stones, air—which constitute the inorganic world. We have seen how as we proceed up our diagram of sizes (Fig. 3) we pass from the simple molecules to proteins and how a branch seems to occur, the main limb of the figure containing the inorganic, and the side branch the organic things. Where exactly are we to locate the root of this side branch of living objects? What is the size and what is the nature of the simplest living thing? These are questions which, in the light of the traps we have already discussed, we should be wary of trying to answer. Rather let us inquire what kind of things are actually to be found in this borderland region, and so form conclusions on the basis of the facts which are at present available.

Let us begin with the simple unicellular organisms—amoebae, yeast cells, and similar creatures, mostly of approximately the size of a red blood cell, that is to say, situated at about point 14 in our scale, although some may be substantially larger. These unicellular organisms are completely alive in every sense of the word. They grow and divide into two, reproducing their like; they take in and assimilate food, they have a definite internal structure which can be seen under a sufficiently powerful microscope, especially if the cell be first suitably stained. Some of them are able, within limits, to change their form and in this way to move about from spot to spot.

As we go down the scale we come to one-celled organisms of a more curious type, for in the bacteria we seem to have simple little rods or spheres of living matter with little or no visible structure (see Plate VII). Sometimes they may have flagellae which enable them to move through water, sometimes suitable staining may reveal one or two points on the surface

which seem to be distinct from the rest, as they take on a different colour, but for the most part they are too small for even the best microscope to be able to distinguish the structure in any detail. Structure there must be, for, as we have seen, these minute objects—they appear in the region of points 9 to 11 on our scale—are often able to perform remarkable feats of chemical synthesis. They are able to build up proteins and fats and complex carbohydrates from quite simple substances, and so it is evident that they must be very highly organized factories for the production of just the right compound at the right place and time.

Most of us are apt to think of these remarkable creatures exclusively in relation to disease. The very words "bacteria" and "germs" suggest to us diphtheria, cholera, plague, and similar unpleasant afflictions. So much is this the case that there is a tendency to think of bacteriology as being primarily medical bacteriology. We are apt to forget that medical bacteriology is only a particular application of a much wider science, just as the chemistry of dyestuffs, for instance, is a special branch of organic chemistry. The explanation, doubtless, is to be found in the extreme importance of this branch of the subject for the well-being of the human race, and in the fact that the earlier work on bacteriology was chiefly on the medical side. But for every type of bacterium which is the cause of a human disease there must be hundreds which are harmless to the human or animal organism. These harmless bacteria—non-pathogenic is the correct term—are of the most diverse types. Some can live on leather; others can break up cellulose and utilize this unpromising substance as food; others can live in hot springs at temperatures near the boiling-point of water. Others have remarkable powers of producing pigment—one called *B. prodigiosus* manufactures a bright red colouring-matter, and according to some it was the presence of this bacterium that was responsible for the first of the ten plagues of Egypt, water turning into blood (Exodus vii. 20). Such chromogenic bacteria tend to draw attention

to themselves and to be specially studied simply because of the colour they produce, but many other less ostentatious species prove to be just as remarkable in respect of the feats of synthetic chemistry which they can perform.

The bacteria, then, are not all harmful to man and the higher animals; some appear to be neither our friends nor our foes, but quite a number are definitely useful to us. Consider, for example, the soil bacteria, without which our gardens and fields would be barren wastes. These organisms fix the nitrogen from the air and convert it into ammonium salts and nitrites and nitrates, so that it is readily utilizable by the growing plant. They also bring about the decay of dead vegetable matter—old roots, stems, and leaves—so that the organic substances in these are broken down, and the inhospitable soil becomes a rich humus as the result of the admixture of organic material.

Bacteria have been also commandeered by man for his own special purposes: one variety he employs to convert alcohol into acetic acid in the preparation of vinegar; another by acting on milk curds helps to make cheese. Occasionally the easiest way of obtaining some out-of-the-way organic compound is to set a suitable strain of bacterium manufacturing it for us. No doubt in the future the harnessing of these hosts of bacteria and other micro-organisms in the service of mankind will proceed much further than it has done at the present day. The pioneer work in this direction was done before history began to be written, when man first discovered that the juice of the grape and certain other plant preparations readily underwent fermentation and produced an agreeable drink. It is true that the micro-organism in this case was not a bacterium but the much larger unicellular plant, the yeast, an organism also employed in the making of bread. The use of yeast is the earliest known example of the domestication of a micro-organism.

It is only a little more than half a century since the region of the bacteria—the region between points 9 and 13 on our

scale—began to be explored. When man first domesticated plants and animals, he found them very much less suited for his purposes than the highly specialized and carefully selected varieties available at the present day. It has taken him hundreds, even thousands of years of selection, partly unconscious, partly deliberate, to bring them to their present standards. It is likely that with increased knowledge of the world of micro-organisms and with adequate time for their proper cultivation and selection he may be able to train them too to carry out all kinds of special tasks: to act as armies of synthetic chemists manufacturing the special compounds which he may require, just as he at present uses yeast to produce alcohol or the acetic acid bacillus to produce vinegar.

However, up to the present more attention has been focused on those micro-organisms which we have regarded as our enemies—the pathogenic organisms—than on those which are our potential friends. Fear is sometimes a more potent stimulus than hope. Besides, as we pass to smaller and smaller organisms it becomes increasingly more difficult to detect them and to work with them unless they produce some obvious effect, and one very obvious effect is the onset of a disease. When we go much below point 10 on the scale it becomes very difficult to see the objects even with the best microscope, and so if they do not produce a disease or have some other equally readily detected effect they are very likely to escape attention altogether. It is true that the range of the microscope may be slightly extended by the use of ultra-violet—that is, short-wave—light, but the technique is difficult and the extension in range is not, after all, very great.

It is not surprising, therefore, that our knowledge of organisms below about point 9 on the scale, that is, of diameter equal to the wavelength of blue light (400mμ), is almost entirely limited to the agents which cause diseases in plants or in animals. There is, as we shall see later, one very interesting exception to this general rule.

These small particles, then, being too minute to be observed,

even with the help of the most powerful microscopes, were at first known and detected only by their effects—the production of disease. They were called viruses, and so we speak of the virus of rabies, the virus of smallpox, of chicken-pox, of measles, and so on. It was not found possible to cultivate them on ordinary media, like bacteria, and it is perhaps to be expected that such small bodies should grow only under very special conditions—there must be a limit to the smallness of a body sufficiently organized to be capable of the elaborate synthetical operations necessary for the production of its own substance from the components of ordinary bacterial media. That such viruses do multiply in the bodies of the animals and plants which they infect is a matter of common experience. Take the case of influenza: an epidemic of this disease may begin in a small way and yet sweep throughout the whole country, the minute amount of virus by which each patient is infected rapidly multiplying in his body and rendering him a source of possible infection to an almost unlimited number of his fellow citizens.

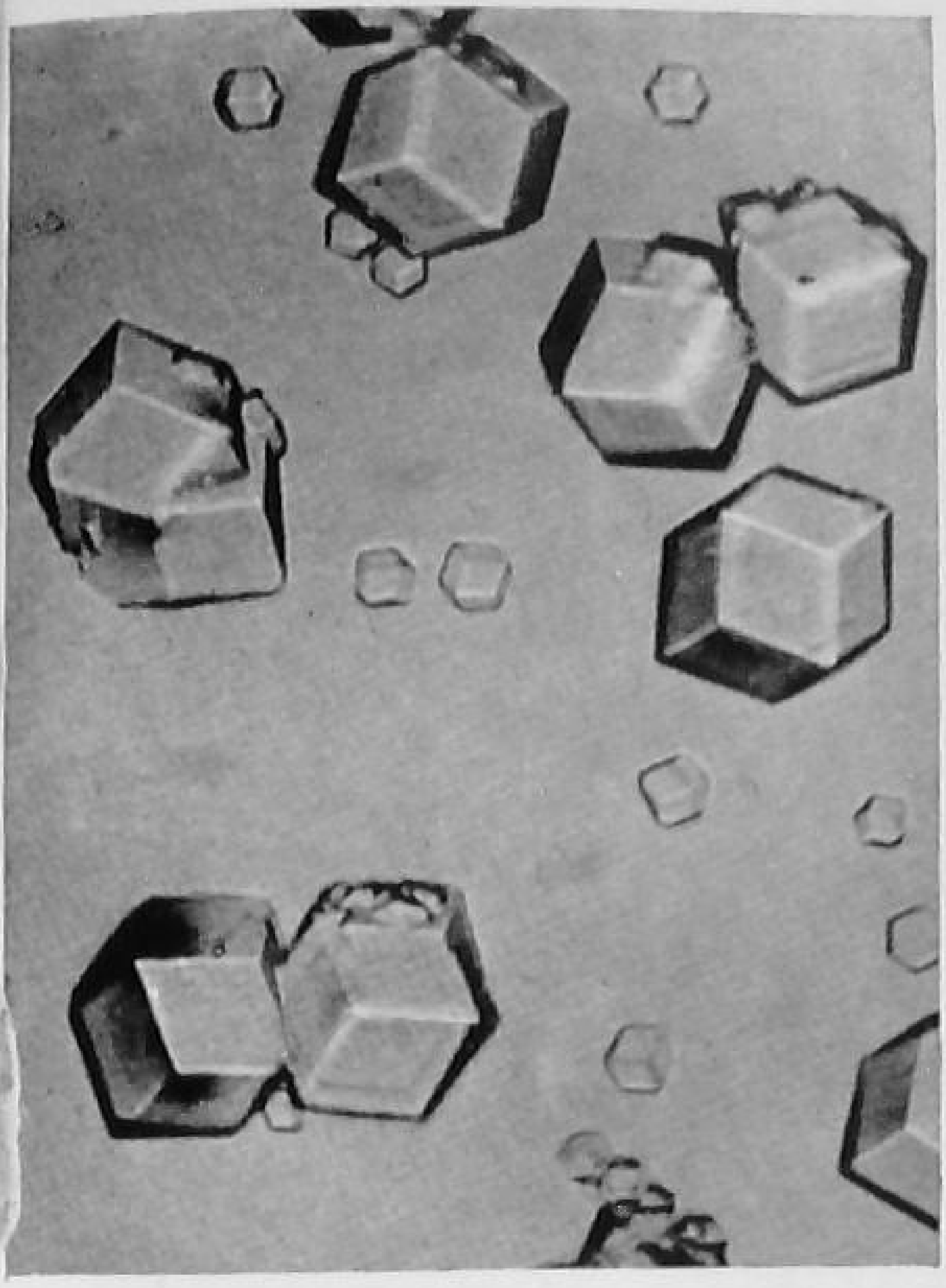
More recently it has been found possible to cultivate certain viruses outside the body under rather special conditions. We have referred above to the fact that cells and fragments of tissue may be cultivated in test-tubes on suitable media. Now it has been found that some viruses will grow and multiply in such tissue cultures, each virus, of course, requiring its special type of tissue on which to grow. So far this manner of cultivation has not been found possible in the case of every virus, but it is probable that in those cases in which success has not yet been achieved it is only a question of discovering the right conditions.

Viruses, then, can be cultivated in the laboratory, but only upon very special media, namely, appropriate living protoplasm. Their synthetic powers are probably very limited and they are more or less parasitic—parasitic in the same sense as human beings, who have to rely on plants for their supply of vitamins and essential amino-acids, only rather more so. For

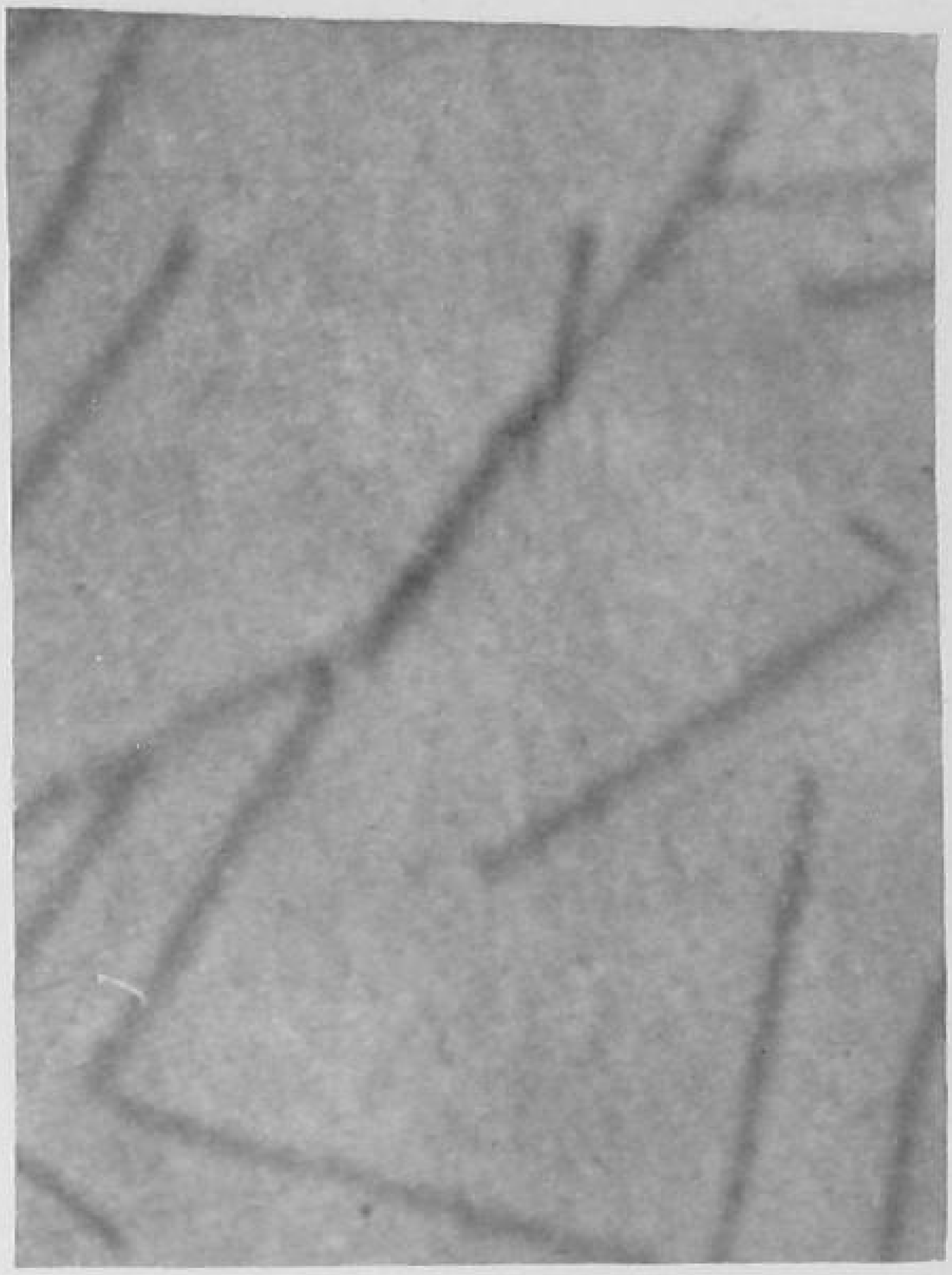
all we know someone may some day discover that he can cultivate a virus on a non-living medium, but it is likely in any case to be a very complex one. Meanwhile we emphasize the fact that these very small agents do possess the power of reproducing their like by a process of growth very similar in its essentials to the growth of larger living beings. To this extent they too must be considered as being alive.

This relationship of the growth of the agent to the living cells on which it grows is particularly well brought out in the exceptional case of an agent which does not cause disease, but which seems to grow on bacteria much as bacteria grow on larger organisms. This agent is called bacteriophage—"bacterium-eater"—for its presence is recognized by the fact that it causes the bacteria on which it has been growing to disintegrate and dissolve into the medium. Bacteriophage, which cannot be cultivated by itself, seems to multiply only on young growing cultures of bacteria. An ordinary bacterial culture becomes increasingly turbid as the number of cells in it multiplies, but if a small quantity of the appropriate "phage" is present, the culture suddenly clears and practically all the cells are found to have dissolved. At the same time the amount of phage has increased very greatly, for a very small quantity of the contents of the tube added to another similar culture of growing bacteria will bring about their dissolution in a similar fashion, and by repeating the process unlimited amounts of the agent can be obtained from an originally small quantity (see Plate VIII).

The fact that phage can grow only on living bacteria is very analogous to the fact that viruses can be cultivated outside the body only on living tissue cultures. It seems natural to classify all these agents together and to regard the bacterio-phages—it has become quite clear that there is not one but a large number of distinct phages—as viruses infesting the cells not of ordinary animals or plants, but of bacteria, which themselves frequently infect the higher

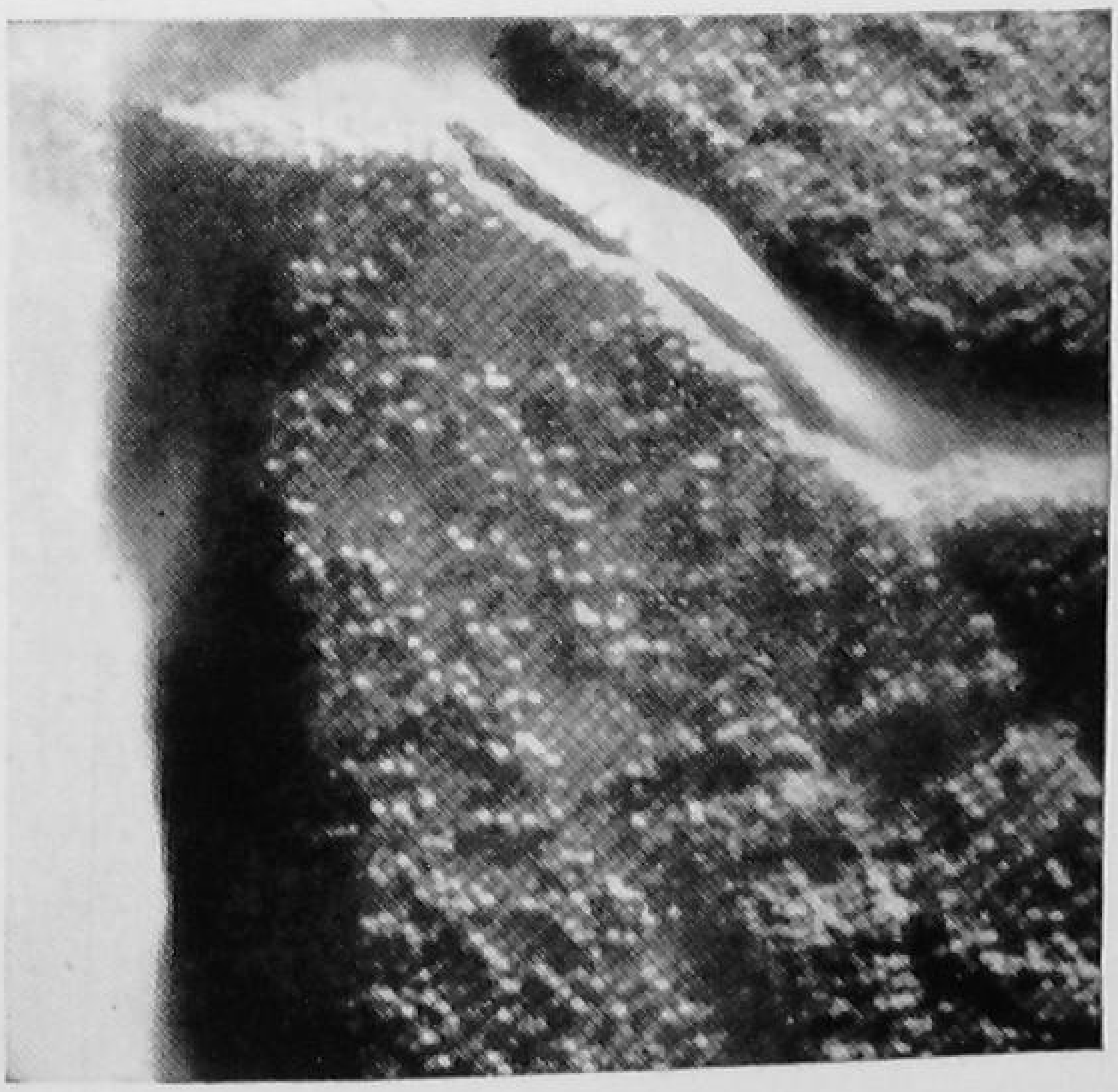


1. Crystals of Bushy Stunt Virus.
× 250.



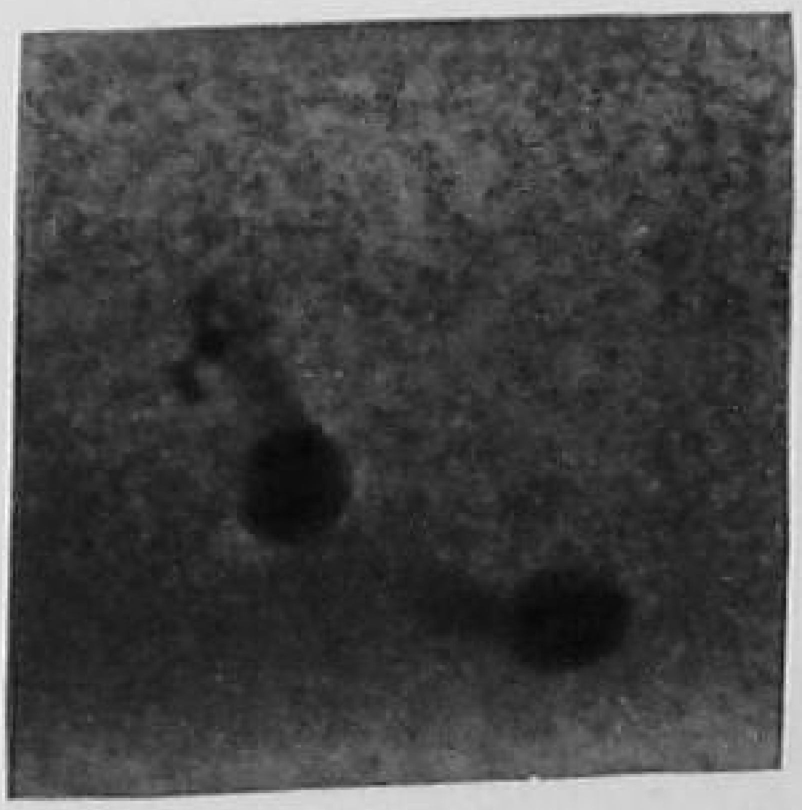
2. Particles of Tobacco Mosaic Virus as revealed by the Electron Microscope.
× 48,000.

(By permission from J. Roy. Soc. Arts.)



3. The Surface of a Crystal of Southern Bean Mosaic Virus, spattered with gold to reveal the separate molecules and photographed in the electron microscope.
× 26,000.

(From Nature.)



4. Electron Microscope of two Bacteriophage Particles. The 'tails' can be faintly discerned.
× 53,000.

(From Topley and Wilson, Bacteriology.)

VIRUS CRYSTALS AND VIRUS MOLECULES.

organisms. We are reminded of the old tag, misquoted from Dean Swift:

> For larger fleas have smaller fleas
> Upon their backs to bite 'em,
> And smaller fleas have lesser fleas
> And so *ad infinitum.*

Up to now we have spoken of the ultimate particles which constitute the viruses or the bacteriophages as being of size less than 9 or 10. This upper limit to their size follows from the fact that they are quite invisible even under the microscope with the highest possible magnification. It is obviously desirable to know their size more exactly; this can be done in several ways, but the method developed by Elford is easy to understand. The principle is that of the sieve; if we wish to know the size of the particles composing, say, a coarse powder, we may take a series of sieves of various meshes and find which one will just hold back the particles in question. This method may be applied even when the particles can only be obtained as an aqueous suspension.

In the case of the viruses the difficulty is that ordinary sieves are far too coarse. We require a mesh diameter of about a hundred thousandth of a millimetre (or a millionth of an inch). The difficulty has been solved by the use of collodion membranes. The adoption of certain precautions in the manufacture of the membranes makes it possible to ensure that the pores in any one membrane are fairly uniform in size. It is possible to prepare a graded series of these and, by testing them on compounds with molecules of known size, to calibrate them so that the pore diameter of each membrane is known. Solutions of a virus (or bacteriophage) are then filtered through these membranes, and it is found which membrane just lets the active agent pass and which keeps it back. The interpretation of the results is not quite so straightforward as one might perhaps expect—in addition to the fact that the holes of the membrane may vary to some extent, there is the further difficulty that the passage of particles through such minute

holes is not a simple mechanical process, but is complicated by the presence of electric charges on the walls of the pores and on the particles themselves. However, these factors can be allowed for, and in this way are obtained the figures given in Table IV.

TABLE IV.—SIZES OF BACTERIA, VIRUSES, AND MOLECULES

Red blood cell	5,000–7,000
Bacillus anthracis	4,000
Bacillus pestis	1,200
Bacillus prodigiosus	750
Psittacosis virus (parrot disease)	275
Rabies virus (hydrophobia)	125
Influenza virus	100
Bacteriophages	25–60
Tobacco mosaic disease virus	30
Haemocyanin molecule	24
Yellow fever virus	22
Foot-and-mouth disease virus	10
Oxyhaemoglobin molecule	5·6
Egg albumin molecule	4
Cane sugar molecule	1
Water molecule	0·3

The figures give the approximate linear dimensions in mμ (one million mμ equal one millimetre). The names of viruses are printed in italics.

These measurements, though only approximate, give some indication of the range of size of this class of substances. In the table the sizes of a few protein molecules have also been given. It will be seen that the smaller viruses are comparable in diameter with the larger proteins.

The viruses, then, may be regarded as very primitive forms of living matter. Like all living things, they are composed of discrete units which multiply when the environment is suitable. It is therefore not surprising that many were sceptical when the American biochemist W. M. Stanley announced that he had crystallized a virus! To those who regarded the animate and inanimate worlds as completely distinct from each other, it seemed inherently fantastic to think that an apparently living thing like a virus could be crystallized. But later work has only served to confirm the essential correctness of Stanley's claim.

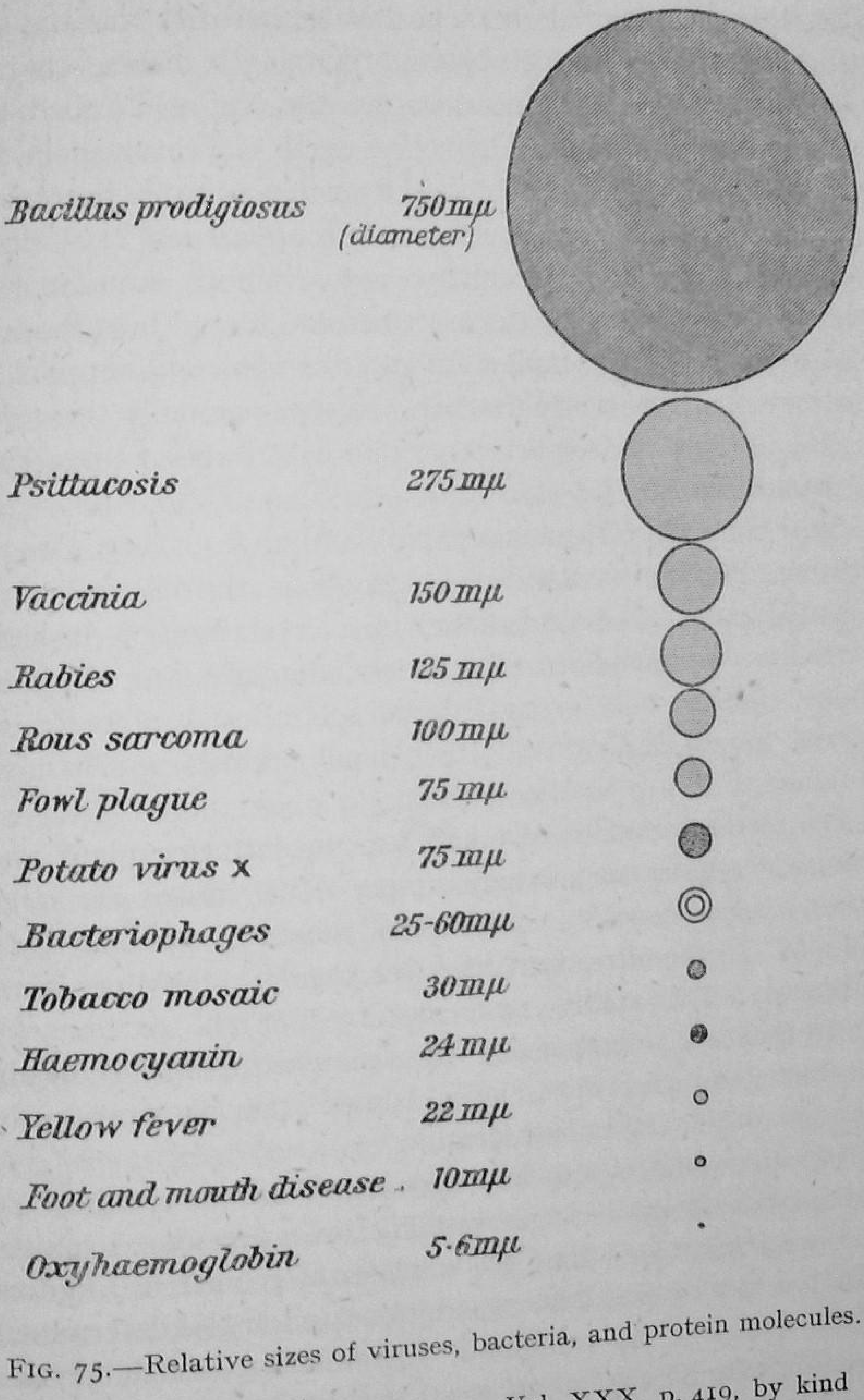


FIG. 75.—Relative sizes of viruses, bacteria, and protein molecules.

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Stanley's original work was carried out with a virus which affected not an animal organism but a plant. It was the one which affects the tobacco plant, producing a disease characterized by a spotted appearance on the leaf and called the tobacco mosaic disease. The active agent is contained in the leaf juice, and by subjecting the latter to a suitable process of purification Stanley finally obtained an apparently crystalline material, a protein, of which a very minute amount was sufficient to produce the disease when inoculated into the leaf of a healthy plant. Stanley advanced evidence in support of the view that this crystalline substance was actually the virus itself—not merely an inactive protein with some of the active agent adsorbed on it.

Since Stanley first announced his startling discovery, viruses causing diseases in other plants such as the cucumber or tomato, have also been isolated in a crystalline or at least partially crystalline form. The American investigator Wyckoff claims even to have separated the agent responsible for an animal disease, the virus of rabbit papillomatosis, and to have obtained it as a crystalline protein.

The method used by Wyckoff for concentrating plant and animal viruses is surprisingly simple. The viruses are large protein particles with a "molecular" weight of ten to twenty millions. In the ultra-centrifuge (see page 78), therefore, they sediment fairly rapidly, more rapidly than the proteins by which they are accompanied. They may in this way be easily concentrated, whereupon, it is claimed, they spontaneously separate in the crystalline form.

Now there are crystals and crystals. When we speak of an ordinary compound being crystalline, we mean that it exists in a solid state, and that the solid forms geometrical figures with flat faces which have orientations and angles determined by the nature of the compound. Examination of such crystalline solids by X-rays has shown that the atoms and molecules which compose them are regularly arranged in a three-dimensional pattern—the emphasis here is on the number three.

In a liquid, on the other hand, there is no such regularity, the molecules are in constant and more or less random motion and orientation, though groups of neighbouring molecules may show from time to time a partial and fleeting regularity. But between the liquid state and the crystalline, we sometimes encounter an intermediate state of matter—the so-called liquid crystals. These exhibit some of the properties of crystals; their molecules, as shown by their action on light and X-rays, are arranged with some regularity, but to ordinary inspection they look more liquid than solid. They lack the rigidity of proper crystals. The regularity or pattern in these liquid crystals must be less perfect than that in ordinary crystals, and it turns out that the pattern instead of being three-dimensional, repeats itself in only two dimensions, or perhaps even only in one. We might, for example, have sheets of regularly arranged molecules, these sheets being arranged parallel to each other, but with no strict relation of the position of the pattern in one sheet to that in the next. Thus the sheets might easily slide over each other, and a mass of such "crystals" would evidently exhibit some plasticity and look like a liquid.

It is now generally agreed that many plant virus "crystals" are of this kind. The X-ray examination shows that the regularity is not a perfect three-dimensional one. The particles of some of these viruses are very long in proportion to their cross-section, and it is not difficult to see that such long pencil-shaped units are likely to lead to the imperfect patterns which give rise to liquid crystals. But not all viruses form long slender particles; the virus which is the cause of the disease in tomatoes known as "bushy stunt" has particles which are as near as maybe spherical. This virus forms crystals which are rhombic dodecahedra (see Plate VIII) and these crystals, under favourable conditions, may grow until their diameter is about one millimetre.

The size of the spherical particles of "bushy stunt" virus can be measured with comparative accuracy. They turn out to have a diameter, when dry, of 26mμ, and their molecular

weight is about $7\frac{1}{2}$ million. The crystals separating from aqueous solution contain three parts of water to every four parts by weight of virus, and some at least of this water may be very intimately associated with the virus molecules. The long thin particles of viruses, such as the tobacco mosaic virus, are not so uniform in size, for their length varies according to treatment, and may even vary from particle to particle in the same sample. Many authorities, such as Bawden, believe that such particles are not individual virus molecules, but that each particle consists of a number of molecules arranged end on end, the number varying according to the length of the particle. The true molecular weight of such viruses is probably less than the tens of millions which would correspond to the particle.

The particles of virus are, of course, too small to be seen with an ordinary microscope. This is not because ordinary glass lenses could not be made powerful enough to give sufficient magnification, but because a virus particle is very small compared with the wavelength of visible light, and so the light with its coarse grain cannot possibly reproduce the size or shape of a virus particle. We might as well try to construct a life-sized model of a mouse out of bricks. If we use sawdust instead of brick, our task becomes possible of performance. The small grain of the sawdust allows us to represent any feature of the anatomy of the mouse that is large in comparison with the grain of the sawdust. Thus, our model could represent its ears and nose and eyes, and even its teeth, but not the individual hairs on its skin. Now the development of physics has allowed us to replace visible light by an instrument of much finer grain. We do not mean X-rays: X-rays consist, it is true, of light of very fine grain, and X-ray analysis has allowed us to "see" the structure of crystals with great success. But X-rays unfortunately cannot be focused as visible light can, and so the "seeing" is not direct, but involves elaborate calculations which at best are only a partial substitute for a focusing lens. The discovery that electrons behave in part like waves, and indeed like waves of length extremely small even

in comparison with X-rays, revealed the possibility of using a stream of electrons for observing small objects, in the place of a ray of light. Now a beam of moving electrons can be bent by an electric or a magnetic field, just as a ray of light can be bent by a prism. This makes it possible to focus rays of electrons by the proper use of electric or magnetic fields. The practical application of these general ideas involves many technical difficulties, but these have been successfully overcome, and the electron microscope is now an article of commerce. With it, magnifications of 50,000 or 100,000 may be obtained. The best optical microscopes magnify at most 1,000 times. The grain of the electron waves is so fine that this grain is no longer the limiting factor; the limit is now set by the imperfection of the electric or magnetic "lenses". Such an instrument reveals details of the structure of cells and micro-organisms and of minute particles previously beyond human observation. The individual particle of a virus can be photographed (see Plate VIII) and its approximate shape and size made apparent. No doubt, as the electron microscope is further improved, it will reveal still finer details of the structure of matter in the "no-man's-land" of colloids, viruses, cellular architecture, and protein molecules.

And now a few words on the chemical nature of these crystalline viruses. Like other proteins, the viruses, when suitably split up, are found to contain amino-acids. But they contain something more. There is always present some phosphorus, a special sugar called ribose, and nitrogenous compounds belonging to the class of purines and pyrimidines (Chapter XVI). This combination of purine, ribose, and phosphate is characteristic of nucleic acid, a constituent of all ordinary cells and one undoubtedly of great importance in cell metabolism and growth. This nucleic acid is present in no mere trace: it constitutes anything from 5 to 15 per cent of the dried virus, and one species is known which contains 40 per cent.

Nucleic acid was so named because it was thought to be characteristic of the nucleus, or central core of the cell which

controls division and is the main repository of genetic inheritance. This substance, it now appears, is not limited to cell nuclei. Like the proteins themselves, it acts both as a structural component and as part of the metabolic mechanism. It can scarcely be without significance that wherever we find the process of multiplication, the division of the cell, the reduplication of the virus molecules, we are confronted by the combination of protein and nucleic acid. These two cell components seem indeed to form the warp and woof of the web of life.

All strange things begin to seem natural once we are accustomed to them, and crystalline viruses are no exception. Already they have become respectable and are accepted in the best scientific society. Why, after all, should viruses not crystallize? As we have already seen, many proteins crystallize. These have usually a molecular weight of the order of one hundred thousand. Some of the smaller viruses are only a few times as heavy. The crystalline viruses which have been most fully investigated are perhaps one hundred times as large. This increased size might be expected to make crystallization somewhat more difficult, but, on the other hand, it must be remembered that the virus as an agent of disease is highly specific, with peculiar and characteristic properties, and that it is therefore to be expected that all the virus particles will possess practically identical structures. It is little wonder that this multitude of particles, all alike in shape and size, easily arrange themselves in a regular pattern, just as do the molecules of cane sugar when they form the crystals that we buy from the grocer.

In the light of these facts, then, we must regard the viruses as occupying a region between the ordinary living microorganisms on the one side and the crystalline compounds of organic and inorganic chemistry on the other. They are dwellers in a kind of no-man's-land, on the one side of which only simple inanimate objects are found, but which, if we cross it, leads to all the varied and innumerable forms which

we class together as living things. There would seem to be no hard-and-fast boundary between these two worlds. The transition is a gradual one—not like passing, say, out of France into Belgium, but rather like sailing from the North Sea to the Atlantic Ocean: no one can say where the boundary is crossed.

It would be a mistake to imagine this zone as occupied only by the viruses and phages. Various complex proteins fall within the same region. There is, for example, haemocyanin, the copper-containing protein which plays the same part in the crab as haemoglobin does in our blood, and there is the still larger thyreoglobulin, the protein occurring in the thyroid gland, within which the active principle, thyroxine (see p. 173), is combined.

It is, however, with the enzymes that the viruses and phages show most affinity, although the enzymes in general have somewhat smaller particle sizes than these giant proteins. Indeed, if there happened to be an enzyme which acted on living cells so as to break them up, and in doing so liberated large quantities of the same enzyme, then this enzyme would be practically indistinguishable from a phage for that type of cell.

Now this is not altogether mere speculation. The American biochemist Northrop has already experimentally demonstrated a closely analogous phenomenon. The protein-digesting enzyme "trypsin" is secreted by the pancreas in an inactive form called "trypsinogen". This can be obtained in crystalline form, and the product when pure is entirely without action on proteins. But it is itself a protein, and it so happens that it is turned into the active trypsin when it is subjected to suitable mild chemical alteration. This is effected by the action of trypsin itself. Thus, the addition under suitable conditions of a minute trace of active trypsin to a solution of inactive trypsinogen soon results in a rapid increase in the amount of trypsin present. The new trypsin in turn acts on the still unaltered trypsinogen, and so the production of the active enzyme goes on at an ever-increasing rate as long as there is

sufficient food—that is to say, trypsinogen—to feed the active agent, the enzyme. Northrop points out how similar the growth of trypsin in such a solution of trypsinogen is to the growth of bacteria in a culture medium—or to the growth of rabbits in Australia, for that matter. Nothing happens until the first bacterium or pair of rabbits is introduced. After that growth goes ahead at an ever-increasing rate until finally it begins to be held up by the failure of the food supply or the otherwise unfavourable nature of the environment. In this production of enzyme from its inactive precursor we have a model of living growth—simple and diagrammatic, but perhaps not fundamentally different from the real thing.

Crystalline proteins, enzymes, phages, viruses, bacteria—so the series seems to run. But let us remember that the first bacteria to be investigated were the harmful ones and that it was only later that the less troublesome species were given much attention. In the same way it is obvious that attention has been directed to the known viruses because they attack man himself or some plant or animal in which he is interested. But many non-pathogenic bacteria are known—why not non-pathogenic viruses? Perhaps they might be found if they were searched for: the difficulty is to know how to search. The individual particles are too small to be seen and identified under the microscope; whilst being presumably proteins themselves there is usually little hope of their being separable from the variety of other proteins with which they are admixed. Yet for all we know living cells may be infested with non-pathogenic viruses—if we may be permitted to use this contradiction in terms. We may all be harbouring these agents and transmitting them to one another and be all the time unconscious of their presence, just as we are usually quite unaware of the many harmless bacteria in our mouths and on our skins. But if we admit this apparently harmless conclusion, then we may be tempted to speculate further.

The known viruses cause diseases of greater or less severity, ranging from rabies and smallpox, on the one hand, to

influenza and the common cold on the other. We now have to contemplate a possible group of entirely harmless viruses. One naturally goes on to wonder whether intermediate ones do not exist; ones not exactly without any effect, but producing disturbances so mild that they tend to be neglected or put down to the state of the weather or of our bank balance or the political situation. But may not these sensations of feeling slightly depressed, or of being rather out of condition, be really due to infection with a very mild virus? And if there may be depressing viruses, why not exhilarating ones, ones which give their victims "that Kruschen feeling" or that sensation of uplift and high endeavour so dear to the revivalist in Tennessee or South Wales?

Now, troubles like measles and influenza tend to come in epidemics. In a similar way we might expect that our virus of mild depression or of mild exaltation would also come in epidemics. Imagine what the result would be on business or on the Stock Exchange. The exaltation virus is prevalent: everyone is optimistic, markets are buoyant, prices soaring. But gradually the population becomes immunized, tempers become less sanguine, and then suddenly the virus of depression sweeps through the country. Bankers and business men, financiers and politicians all tend to catch it; gloom becomes the order of the day; prices fall, governments crash, banks fail, and dishonest financiers are found out. Perhaps some day the medical history of booms and depression may be written on lines such as these—who can tell?

Whatever it may ultimately prove to contain, the region in our scale of size from point 5 to point 9 or 10, this no-man's-land between the things we can see under the microscope and the well-behaved molecules of ordinary chemistry, is unusually difficult to explore, and at the same time it promises a rich reward to those who ultimately succeed in finding out its secrets. For it would seem that it is here, if anywhere, that the clue to the mystery of living things is to be found. It is somewhere in this region that we first meet with objects which

no one would deny were alive. Already the number of atoms in each particle is so great that the molecular architecture can be very elaborate. Exquisitely delicate and complicated structures are possible. The particles, too, are just of the right size for surface forces to exert their maximum effect, and these latter help to promote and control the great variety of chemical reactions on which organized living cells are dependent. The difficulty to the proper understanding of this region is just its essential complexity; but it is this very complexity which makes possible the remarkable thing we call life.

CHAPTER XIX

THE RETREAT FROM THE VITALISTIC

WE are so accustomed to the distinction between living and non-living things, between the organic and the inorganic worlds, that we are apt to forget that this contrast only made its appearance in human thought at a comparatively late stage in the development of society. Primitive man, when he began to think at all, made no such sharp distinction. To him there were spirits of the woods, of the mountains, and of the clouds —spirits which could think and love and hate just like the spirits he thought of as existing within the bodies of his fellow men. Objects within which specially powerful spirits lived had to be worshipped and propitiated, so that their favour might be obtained or their enmity avoided. Even in Europe as late as the Middle Ages the average inhabitant would seem to have thought of himself as living in a world crowded with angels or demons ever ready to help or to hurt him. Belief in sorcery and witchcraft was natural, nay, inevitable under these circumstances; it fitted into the prevalent philosophy of life.

But with the Renaissance and the gradual development of scientific thought from the sixteenth century onwards, all this began to change. It was in astronomy that progress was most rapid and the discoveries most fundamental. It had, of course, been long realized that the motions of the sun and the moon, the stars and the planets in the heavens, could be described in terms of more or less complicated curves, and up to a certain limit it was possible even to predict their future courses. The stars were relatively simple in their behaviour: they described circles round the Pole Star. The sun also revolved round the Pole Star, but had a superimposed north-and-south motion. It was in the motions of the moon, and especially of the planets

Venus, Mercury, Mars, Jupiter, and Saturn that the complexities were greatest. They described curious, complicated curves in the heavens, and in respect of its motion each seemed to be a law unto itself.

But Copernicus and Galileo realized that the whole picture undergoes a radical transformation and simplification if the sun, and not the earth, is regarded as the fixed centre of things. The earth then rotates round its own axis; the moon revolves round the earth; and the earth, in turn, along with the other planets, describes a nearly circular orbit round the sun. Kepler found that the rates at which the various planets move in their orbits could be stated in a very simple law, and the climax in this process of simplification was reached when Newton discovered his Law of Gravitation, and showed that the motions of moon and earth and planets—not only their crude orbits, but their exact paths, as accurately as observations could tell—all were the result of a few very simple laws of motion, as applied to bodies which attracted each other with a force which varied according to the inverse square of the distance. The picture had previously been a mass of meaningless curves, but by looking at it from the proper angle its plan had suddenly become clear; and the astronomer henceforth felt that he "understood" the motion of the planets and that it only required the exertion of sufficient effort to enable him to predict their courses for hundreds or even thousands of years.

These fundamental developments in astronomy were accompanied by discoveries having the same rationalizing effect in other branches of Natural Philosophy. The fundamental laws governing the equilibria of gases and liquids were discovered. The science of optics made rapid advances. By the end of the seventeenth century the scientific era had definitely come to life as a vigorous youngster, still undeveloped and quite diminutive in size, but full of promise for the future and evidently destined to make a great impression on the world at large.

However, in branches of Natural Philosophy other than astronomy and physics not much real progress was achieved until the eighteenth century was well on its way. In sciences such as geology and chemistry observations and facts accumulated, but these branches of knowledge were in the same state as astronomy before the days of Copernicus. The proper angle from which to regard the picture had not yet been found. And this could not easily be done until misleading ideas and prejudices had been cleared away. The believers in a fixed earth of the sixteenth century had their chemical counterpart in the "phlogistonists" of the eighteenth. Lavoisier, however, showed that combustion does not consist in the expulsion by heat of a substance called phlogiston from the combustible material, but in the combination of the latter with a component of the atmosphere, the gas we now call oxygen. By the end of the eighteenth century the ground had been cleared for the development of the modern theory of the molecule and the atomic structure of matter. The hypothesis was advanced by John Dalton, a schoolmaster of Manchester, that every chemical element consisted of a large number of atoms, all alike, and that these different kinds of atoms were capable of combining according to certain definite rules embodied in the idea of valency; by this hypothesis it was at once possible to correlate a large number of facts, the facts of inorganic chemistry. Chemistry, like physics and astronomy, was seen to be built on a plan, perhaps a somewhat complicated one, but definite and comprehensible.

At this stage in the history of science, there appeared to be a deep-seated division of substances into two great groups. One group included all those compounds found in the inorganic world, salts and metals, air and water. It was within this group of substances that the methods of chemistry, as it then was, had proved fruitful, and the atomic theory of Dalton had created order out of a chaos of empirical facts. But, apart from these inorganic compounds, it was realized that there was a large number of substances apparently of a different

kind, the substances which never appeared except in living things or as a result of the activity of living things. These "organic" compounds, it was known, contained elements such as carbon, hydrogen, and oxygen, found in a free or combined state in the inorganic world, but all efforts to produce an "organic" compound out of inorganic ones without the use of living organisms had met with complete failure. In these circumstances the division of chemistry into two sections, organic chemistry and inorganic chemistry, seemed well justified, and this in turn supported the view that the phenomenon of life was a thing separate and quite distinct from, though superimposed upon, the inorganic world of land, sea, and air.

Indeed, at this stage the evidence in favour of a dualistic view of the universe might well have seemed overwhelming. Not only was it supported by Biblical authority—was not the earth made on the third day, and the vegetable and animal kingdoms brought into existence subsequently as distinct creations?—not only was it in accordance with plain simple common sense, just as the obvious fact of the sun rising in the east and moving across the sky to set in the west had been three centuries previously; but there was the very important conclusion, based upon innumerable experiments, that the "organic" world was characterized by a special group of compounds out of which it was made and which it alone seemed able to synthesize.

It was the German chemist Friedrich Wöhler who in 1828 made the epoch-making discovery that urea could be synthesized from materials of unquestionably inorganic origin. Urea, of course, is a very simple and common compound. It had long been known as a constituent of urine and recognized as a waste product of the animal body. But up to this time it had never been obtained except as the result of the activity of living matter. It was recognized by general consent as a typical "organic" compound. It was therefore commonly believed that it would prove impossible to synthesize it in

the laboratory. But the apparently impossible was achieved, and the first shattering blow given to the attempt to draw a fundamental distinction between organic and inorganic compounds.

The process of synthesizing organic compounds, begun by Wöhler over a hundred years ago, has gone on continuously at an ever-increasing speed. One after the other, substances of greater and greater complexity have been synthesized by the organic chemist. Of course the chemist does not always start out from the actual elements, carbon, hydrogen, oxygen, and so forth; it is enough if he can produce a new compound from substances previously synthesized. He knows that if he really wanted to do so he could make any one of these thousands of natural products from its elements; it would only be a question of being able to devote sufficient labour and expense to the work. Even in the case of those natural products, such as strychnine or cholesterol, which have not yet been synthesized, the exact constitution is frequently known, and success in synthesis is dependent only on hitting on the right experimental conditions and following the right route. It is true we still give separate courses of lectures on organic and inorganic chemistry at our universities and colleges and still have our text-books of chemistry named accordingly, but this is a matter of convenience and sometimes the border-line is hard to place.

From the time of Wöhler right up to the present day the history of organic chemistry is largely the story of the working out of the structure of one after another of the extraordinary variety of substances found in plants and animals, and, in a very large number of cases of their synthesis by the methods which have been developed in the laboratory during the past hundred years. These methods, as we have seen, are often crude and inefficient, but in practice they have shown themselves of extremely wide applicability, and as time has gone on and new and more difficult problems have arisen, new methods have been devised and old ones improved so that it

would be rash to set any limit to the ultimate possibilities of synthetic organic chemistry.

It was naturally the simpler compounds that were first prepared synthetically—paraffins, alcohols, acids, and similar substances of small molecular size and not very complicated structure. But as time went on and experience increased, more ambitious tasks were attempted and in due course successfully accomplished. In 1869 Gräbe and Liebermann in Germany and Sir W. H. Perkin in England published almost simultaneously the first synthesis of a naturally occurring dyestuff, alizarin, the compound present in the madder plant. Synthetic dyestuffs of various kinds had been known for one or two decades, and the great industry of the manufacture of synthetic dyestuffs was already in vigorous growth, but this was the first time that the laboratory chemist had actually made the precise colouring substance produced by nature. A decade or so later Baeyer had synthesized another and even more important natural dyestuff, indigo. In both these cases the methods of the organic chemist proved in the end to be more efficient from an economic point of view than the old process of cultivating the plant and extracting the dye therefrom, and so the cultivation of the madder plant and the indigo plant has been almost completely superseded by the chemist and the chemical factory.

Other classes of natural products were also being intensively investigated and their structures ascertained. In about 1882, Emil Fischer applied himself to the problem of the structure of uric acid and related compounds. In a few years the main problem had been solved, and uric acid itself was synthesized (by Behrend and Roosen) in 1888. Fischer went on to his illustrious work on the sugars, in which the basis was laid of the chemistry of this important and extremely complex group of substances, and incidentally the synthesis of many of the simpler ones achieved. About the same time another large group of compounds, the terpenes, was intensively investigated, and the synthetic work of W. H. Perkin, junr., on these

substances, characteristic of turpentine and other essential oils, is a model of its kind. Alkaloids, too, were investigated, and one after another were synthesized. Sometimes the task was a comparatively easy one; occasionally it was extremely difficult; and even to-day some of the commonest alkaloids have defied all attempts at their synthesis.

The twentieth century has seen the continuation of the advance which the nineteenth century began—only the rate of progress has become faster and faster. New compounds, indeed, whole new classes of compounds, have been discovered and their composition elucidated. Sometimes these are present in only exceedingly minute amounts in the animal or the plant, but they are of such extreme physiological activity that their presence in just the right concentrations is of vital importance to the organism. The failure of one contact in a magneto will upset the smooth running of the whole engine, and may easily lead to complete disaster. As we have seen in Chapter IX, the living organism, if deprived, for example, of its minute supply of thyroxine, soon begins to misfire and to work extremely inefficiently or not at all. Our health and our happiness, our emotions and our desires are effectively controlled by traces of these extremely potent substances. Our physical well-being, our power to think and reason, our whole attitude to life, whether gloomy or sanguine, despondent or buoyant—all these are definitely dependent upon the presence of these potent compounds in the right places at the right time and in the right amount. But they are in no way magical substances. They are just ordinary molecular structures—most of them can be crystallized, some have already been synthesized. We can no longer think of the vitamins and hormones as peculiar or mysterious "principles".

But living matter is not merely a mass of compounds thrown together in a random fashion, any more than a house is merely a heap of brick and plaster and logs of wood. It has a definite structure. The units out of which it is made have to be built up according to definite patterns. The structures so produced

are themselves arranged in larger aggregates which are in turn parts of a greater whole. Thus, as we have seen (Chapter V), the amino-acids are built up into proteins and the simple sugars are associated together to give starch, glycogen, and cellulose (Chapter VI). These, in turn, are constituents of the cells out of which the organism is built up. Now it is in the intermediate region between the simple molecules on the one hand and the microscopically visible cells and cell structures on the other that the problem of finding out the architecture of living matter is most difficult. For long this no-man's-land —from about 5 to 10 on our scale of sizes (p. 9)—seemed likely to resist all attempts at detailed investigation. It is true that colloidal chemistry came to life under the inspiration of Thomas Graham over one hundred years ago. This branch of chemistry has gradually developed and has proved to be of great importance both in biology and in industry. But papers on colloids have tended in the past to leave one with the impression that they were working round the problem rather than getting to the root of it. They told us what certain colloid substances did and formulated laws as to how they reacted with each other, but on the whole they failed to interpret these laws in terms of the fundamental properties of atoms and molecules, that is to say, in terms of the structure of the colloidal substances.

The reason for this is a very simple one. Little was known about the precise structure of these colloidal substances, for they are not amenable to the ordinary methods of organic chemistry, and besides, they are essentially highly complex. The problem is indeed a difficult one, yet until it has been solved no adequate understanding of living processes will be possible.

Of all these colloidal substances the proteins stand out as the most important and at the same time the most unpromising from the chemical point of view. The great variety in appearance and properties which is so characteristic of these substances, the difficulty of treating them by the ordinary

methods of organic chemistry—their disinclination to crystallize and their complete refusal to distil and, above all, the extreme instability to heat and many other reagents which most of the proteins exhibit—might suggest that the pre-Wöhlerian theory was true in a somewhat modified form. Everyone now agrees that no real division exists between the inorganic and the ordinary organic compounds, but are not the proteins essentially different from all other compounds, organic and inorganic alike?

At the beginning of the present century our knowledge of protein structure was very vague and largely speculative. The first great advance was made by Emil Fischer during the early years of this century, and his conception of the protein molecule as essentially a long chain of amino-acid molecules, linked together in a characteristic manner, has formed the basis for practically all subsequent work. Every year many new facts are being discovered, and as the result of piecing these together and working out the implications of the observations our knowledge of the protein molecules is gradually becoming more precise and more certain.

No one can pretend, of course, that we have a complete knowledge of even the simplest protein, but there is little doubt that the molecules of proteins, like those of simpler substances, are composed of atoms united into a definite structure and that the properties of the protein are capable of description and explanation in terms of this structure. In fact, these complex and mysterious molecules differ from the simpler ones with which we are so familiar in much the same way as an elaborate treatise differs from a short statement of, say, ten or a dozen words. Both are in the same language, employing the same kind of words, and these in turn are drawn from the same alphabet of letters. The same rules of spelling and grammar determine how these letters and words are to be put together. But if we are familiar enough with a language to understand most simple statements without difficulty, we may be fairly sure that with sufficient effort and

time we could master even a very elaborate and complex document. It is the same with the proteins—the particular details of the structure are in many respects still obscure, but the underlying principles are fairly completely known and with further study and experiment our understanding of them will become more and more complete.

The analogy of molecular structures to documents composed in some particular language brings out a point of great significance. Sentences, chapters, treatises—these consist of words and in the last analysis of letters. But quite obviously they are not merely collections of words or letters; to have any meaning these must be arranged in a suitable order, so that they bear particular relations one to another. Now, though the letters and words are indispensable, it is these relationships which give meaning to the whole; the interchange of two words or even of two letters might profoundly alter the meaning. The skilled writer gets his effects, not by introducing new letters or inventing new words, but by weaving together common words into new and often highly complicated relationships. The words, the sentences, the whole structure of the book and its meaning—these are all determined by the innumerable relationships which exist between the individual letters, and these relationships are the really vital characteristics. In the same way, molecules and, more generally, all material structures, are composed of atoms—ultimately, if we prefer it, of protons and electrons—associated together into particular and definite structures. Such structures imply the existence of relationships, and it is these sets of relationships which really distinguish one structure from another. In a molecule, say of benzene, we could imagine all the electrons and all the atomic nuclei replaced by others exactly similar. The molecule would evidently remain unaltered in its properties, and would clearly be indistinguishable from the original one. It would, in fact, from the physical point of view, *be* the original one. It is like a car of which every part is in time replaced by a new corresponding part—engine, body, hood,

wheels, until only the steering wheel is left and finally even this is renewed. Is it still the old car covered by the same registration and licence fee or is it a new one? The problem in the case of the molecule is even more subtle, for all electrons and all protons are absolutely alike and not just approximately so. The "new" molecule agrees completely with the "old" both in its internal structure and in its relations to external objects. As the exchange could not be detected experimentally, we should undoubtedly regard it as the same molecule in spite of the fact that from the purely "material" point of view, it was entirely new. What has remained unaltered is the set of relationships which characterize this particular molecule; these relationships are really the essence of the molecule.

What is true of a simple molecule continues to hold for more complicated structures. The important and characteristic thing about a protein molecule is not the actual atoms of which it is composed, but the relations between these atoms, the pattern which they form. The same is evidently true of organized structures such as cells, or whole organs such as kidneys or brain. Indeed, it is equally true of the whole animal or a man. You, for example, are a material structure composed of a very large number of perfectly ordinary atoms. But the essential point about you is not these atoms but a complex set of relationships between them. These relationships are principally internal ones, but they also include relations with the outside world, and frequently these latter are far from negligible. As time passes the individual atoms in your body are gradually replaced by new ones derived principally from your food and drink. Over three-quarters of your body consists of water, and experiment shows that this is almost entirely replaced in the course of a few weeks. The renewal of some other constituents of the body is a slower process, but, apart from the comparatively lifeless structures such as parts of the bones and teeth, there are probably relatively few atoms still in your body which were there twenty years ago. And yet you still look upon yourself and

are looked upon by your friends and neighbours as the same person.

What has remained constant is evidently not the material atoms of which your body is composed. The basis of continuity of an individual is to be sought rather in the persistence of particular relationships between the atoms. The individual, indeed, is to be identified with the aggregate of these relationships rather than with the atoms between which these relationships exist.

Let us at this point indulge in a little speculation. We may suppose that someone with superhuman powers is able to piece together another collection of atoms in exactly the same relation to each other as exists in the case of some particular person, say Mr. Winston Churchill. The new Mr. Churchill would presumably look the same and do much the same as the old. In fact, if the set of relationships is the really characteristic thing, there should be no essential difference between the two men. They would, of course, be slightly different in one respect, namely, in that they could not occupy the same space at the same time, and so, though the internal relationships of the atoms among themselves were the same in both organisms, their relations to the outside world would necessarily be different. Furthermore, though the two beings would in general do the same things, it does not follow that under apparently identical conditions they would always do exactly the same thing at the same time. The principle of indeterminacy comes in here. The two Mr. Churchills would be alike in the same sense that two atoms are alike. Their behaviour would be predictable only in the statistical sense. If both were subjected to the same test a great number of times—say, offered the choice of a large cigar or a magnum of champagne —the proportion of cases in which one reacted in some specified way would be the same as the corresponding proportion for the other individual, but there would be no guarantee that both would do exactly the same thing at the same time.

This unpredictability of behaviour is closely connected with

the principle of indeterminacy. There seems to be no physical method by which we could even in theory determine the position and velocity simultaneously of the various particles of which we consider the body to be built up. This vagueness in the data completely invalidates any calculation of future behaviour in the sense of Newtonian dynamics. Now the interesting point for our present discussion is that this indeterminacy of the strictly material particles is in no way inconsistent with the existence of precise relationships between these particles. A relation may be quite definite and unambiguous and yet leave much freedom to the things which are related. Thus the relation "*b* is greater than *a*" is a significant and often very important one, and yet is consistent with *a* having any value whatever. And so it is with material bodies, living and non-living alike. What is precise about them is the set of relationships which defines the mutual interactions of the particles of which they are composed. Within this system of relationships, the individual particles may be replaced by others without the structure as a whole losing its identity, while at the same time there is just enough lack of precision in the system (looked on as a mechanical system in the ordinary sense) to exhibit that indeterminacy and lack of exact predictability so characteristic both of single atoms and living beings.

In the above discussion we have been gradually led from the topic of the structure of living beings, and their constituent parts and characteristic products, to a consideration of their activity and behaviour. The facts as to how animals react in specified circumstances are obtainable by direct observation; and with rather more elaborate technique, the same is true of parts of an animal isolated from the body as a whole. This investigation of the function of living structures is broadly the business of physiology; and it is an essential feature of the great mass of facts revealed by this science that they are all of them consistent with the laws of inorganic nature, the laws of physics and chemistry. That is not to say that all

these facts are completely explicable by these laws; it means only that they do not contradict them.

It is, of course, a matter of common experience that living bodies behave in at least some respects just like non-living ones. They are subject to the same law of gravitation—a man flung over a cliff will fall through the air in the same way as a dummy of the same size and weight. An important contribution to this subject was made by Lavoisier, when he showed in the latter half of the eighteenth century that living animals are continually using oxygen, and that the development of heat in the animal body was due to processes of combustion taking place within, essentially similar to the process of inorganic combustion. This ultimately led to the realization that the animal body is in many ways analogous to an ordinary mechanical engine, and in particular that in all the activities associated with life the Principle of the Conservation of Energy is never infringed. We have already seen in Chapter VIII how important, both from a theoretical and a practical point of view, is this conclusion.

As the sciences of physiology and, at a later date, of biochemistry developed, the knowledge of the physical and chemical processes occurring in the living tissues and cells became more and more precise and detailed. Facts of all kinds—mechanical, electrical, and chemical—have accumulated in embarrassing abundance. Observations have been made on animals and tissues of almost every variety and under all kinds of conditions. In no single instance can it be said that there is definite proof that a case has been observed in which the laws of physics and chemistry do not apply.

But it is not merely that living things and living processes conform to the general laws of chemistry and physics; for example, the law of gravitation and the law of the conservation of energy. It is perhaps even more significant that the detailed analysis of these processes reveals, in ever-increasing degree, the existence within the cell of physico-chemical systems which can be isolated in a form demonstrably free from living matter

in the ordinary sense, and yet still capable of carrying out their characteristic reactions. We may recall, for example, how enzyme systems can be obtained in the test-tube, and how the further analysis of these systems is gradually enabling them to be understood in terms of ordinary physics and chemistry. The details are being slowly worked out of the extremely complex series of reactions concerned in the utilization of carbohydrate by the yeast cell or in the muscle of an animal. Many of the chemical transformations involved appeared at first sight to be peculiar, and quite distinct from the reactions ordinarily encountered in the test-tube. However, as knowledge has accumulated the anomalies have tended to disappear, and the picture emerges of a system highly complex and still obscure in detail, but quite obviously similar in kind to those with which we are so familiar in the organic chemistry laboratory.

This belief in the uniformity of all nature, in the essential consistency of all phenomena, living and non-living alike, is indeed an article of faith which supplies the driving-power behind biochemical research. There can be little doubt that if we regard this belief merely as a working hypothesis, it has fully justified itself by the mass of interesting and important results which have already been obtained. Moreover, the failure of any fact to emerge in conflict with the belief is itself a strong support. But it is not proof. Perhaps we cannot expect ever to obtain complete proof of a general proposition of this kind. All we can say is that the more we investigate living structures, the more completely are we able to explain their functions in terms of the molecular structures involved.

But here, perhaps, we touch the crucial point. Some may consider that however satisfactory such explanations may be in regard to detail, they fail to explain the co-ordination of living beings as wholes. And it must be admitted that, broadly speaking, we are still essentially ignorant of most of the really important things that happen even in the simplest living cell. At the same time it would be very rash to assume that, because

the co-ordination of the various parts of an animal or plant is very perfect and mysterious, it is therefore something involving a new order of nature. The remarkable effects of the hormones and especially of the sex hormones, the action of the organizer substance in relation to embryonic development—phenomena such as these demonstrate how quite ordinary chemical compounds help to control the complicated machine. There is even reason to believe that the development of particular organs, such as the lens of an eye or the structure of an ear, proceeds under the control of specific local "organizer" substances. Even our deepest emotions may be conditioned by traces of a derivative of phenanthrene.

It would seem, then, that the result of the development of science in general and of physiology and biochemistry in particular has been to bring about a retreat all along the line from the vitalistic view, which insists that there is in living beings a class of phenomena essentially different from that observable in inorganic nature. In respect of structure the dualistic view has long been out of date, and is now almost universally abandoned. In relation to function the issue is not yet decided, but it is almost in the nature of the case that the vitalists are steadily forced to give up ground.

But will this retreat continue indefinitely? One or two points must be borne in mind when considering this question. It must not be forgotten that the Principle of Indeterminacy sets a limit to the precision with which we can know any given structure; as we say in Chapter III, this limit becomes particularly important when the structure is peculiar or unique. Chemistry as ordinarily understood does not deal with individual atoms or molecules; it is concerned with systems which contain large numbers of equivalent units. Consequently, only in as far as the structural units involved in living systems are not unique but available in large numbers will the science and conclusions of chemistry apply to them. One single muscle or one single brain, in as far as it is an individual structure, could not be completely specified even by

the cleverest scientific superman, and so could not be described in physico-chemical terms either structurally or functionally. Of course, such a muscle or brain will, in fact, have much in common with other muscles or brains, and even in the same organ certain atomic configurations will occur over and over again. Not one molecule of glucose or lactic acid or oxidizing enzyme will be present, but many, even myriads. It is really this fact which has made the development of biochemistry possible.

We may put the point briefly by saying that all our scientific knowledge of the universe is really statistical. What is unique, what happens once only, is of no interest *sub specie aeternitatis*. These unique happenings may, of course, be of great interest to us personally—we are each of us an example of a unique structure exhibiting a sequence of unique events—but it would seem that as such we are not amenable to the scientific method. If we like we may of course call this individual, personal aspect of life "vitalistic": this is only a matter of definition. But it would be a none too happy choice, for the word has already been used with other meanings; and further, as we have seen, this individual, particular aspect also applies to single atoms and molecules as well as to living structures. The contrast is really not between vitalistic and mechanistic, but rather between the particular and the statistical, between the individual and the aggregate.

If this point of view is a correct one, the problem of synthesizing a man is just as soluble as the problem of synthesizing a molecule of alcohol. Of course, the actual task would be a much more laborious one. It took nature at least hundreds of millions of years to work up through all kinds of intermediate forms: through invertebrates and sea animals, fishes, and amphibians, until warm-blooded mammals were produced, to be succeeded ultimately by man himself. No doubt if the synthesis were repeated *de novo* under conscious direction, a considerable saving in time could be effected and short cuts frequently adopted, but the task would unquestionably be a

formidable one, even to chemists with many times the knowledge and resources that we at present possess: but in principle it should not be impossible. It would seem, however, that we could not in any circumstances synthesize a *particular* man—all we could hope to do would be to synthesize men *en masse*. We could then pick out the particular type we required, if we were fortunate enough to have obtained it amongst the others. Even in the simplest organic chemistry we rarely if ever get a yield of one hundred per cent of the substance we want. Moreover, just as the behaviour of a single molecule of a pure compound is not completely predictable, so our synthetic men will be not robots but individuals whose behaviour will be no more predictable than our own. And so with the crowning achievement of a non-vitalistic science will come the final overthrow of a purely mechanistic philosophy.

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